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(Continued)

CHORIOCARCINOMA OF THE UTERUS*

Study of 74 Cases From the Mathieu Memorial Chorionepithelioma Registry†

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THIS paper is based on the unequaled material of the Mathieu Memorial Chorionepithelioma Registry of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons. In addition to a large amount of cognate material, such as hydatidiform moles and other abnormal pregnancy lesions, the Registry makes available to us for study 74 cases of choriocarcinoma. It is to be doubted that any one group has ever previously had the oppor [illegible] of direct study of such a large material. There are of course reports of much larger numbers of cases collected from the literature, but all such collective reviews suffer the disadvantage that they are based on case reports, many of which are of doubtful authenticity.

We have tried to make the present report as nearly a factual one as possible, on the basis of our own material. This is not to be construed as indicating a supercilious attitude toward papers based partly or largely on second-

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hand material from the literature, for many of the authors of such papers have made valuable contributions to the subject. Nor can any one embark on a study of this sort without making full use of the fundamental contributions of such early workers as Marchand,[1] Meyer,[2] and others.

It must at the outset be admitted that our own material also presents certain limitations. It is sent in from clinics and laboratories in all parts of our own and other countries for authentication and classification. Many of these patients had been studied incompletely and inadequately, and in many the microscopic slides and tissue specimens have left much to be desired. Nor could these limitations of some of our Registry material be altogether overcome by extensive correspondence on the Committee's part.

As examples of the inadequacies often encountered, one might mention the incompleteness or total lack of hormone studies in a large proportion of our cases, though this is perhaps not surprising since so many came from hospitals not possessing facilities for such studies. Again, information as to the operative findings, including possible ovarian changes, was usually incomplete. The fact remains that even with these defects our material compares favorably in quality with that available in any collective study of the literature, with the tremendous advantage that a great mass of pathologic material was made available for personal study by a single group of competent pathologists, and with the further advantage of reasonably complete clinical data, and a good follow-up.

For these reasons, it is felt that the chief contribution possible to us in the present study pertains to the pathologic differentiation and the prognosis of chorionepithelioma. After all, these constitute the real core of this whole confused question, so that no apology is necessary for accenting these aspects of the problem in this paper, though we hope also to comment upon some of the clinical characteristics and the management of choriocarcinoma.

It is generally recognized that the notoriously high incidence of incorrect diagnosis in this field is due to the fact that a wrong diagnosis of choriocarcinoma is so often made in certain types of hydatidiform mole, as well as in such non-neoplastic lesions as the so-called syncytial endometritis. The fact that the Registry has collected a large amount of this cognate material has been a very great advantage to us in permitting parallel studies of the malignant and the benign trophoblastic lesions. A study of the latter type of Registry material will be reserved for a later publication, though it will be impossible to avoid comments in the present paper upon the nonmalignant lesions, as they are contrasted with the malignant group.

Before proceeding to the discussion of the pathologic characteristics of choriocarcinoma, two tables may be presented as bearing on some of its clinical features, with no particular comment except that Table I does not appear to bear out the belief expressed by some that choriocarcinoma is more likely to develop in patients with a high degree of multiparity. This latter view has been suggested by some to explain what is apparently a genuinely disproportionate incidence of both hydatidiform mole and choriocarcinoma in certain Oriental countries, notably China and the Philippines.

TABLE I. AGE DISTRIBUTION

Below 20 years	8
20-30 years	41
31-40 years	18
41-50 years	7
Total	74

TABLE II. NUMBER OF PREVIOUS PREGNANCIES

Para 0	20
Para i	18
Para ii	10
Para iii	10
Para iv	3
Para v	1
Para vi	3
Para vii	1
Para viii	2
Para ix	1
Para xii	1
Para xvii	1
Para unknown	3
Total	74

TABLE III. TYPE OF PREGNANCY RESULTING IN CHORIOCARCINOMA

Hydatidiform mole	29 (39.2%)
Abortion	28 (37.8%)
Full-term pregnancy	17 (23%)
Total	74

Table III is of interest as bearing on the statement so often found in the literature that, roughly speaking, at least 50 per cent of choriocarcinomas follow hydatidiform moles, 25 per cent develop after abortion, and 25 per cent after full-term delivery. While our own figures (Table III) do not show a too extreme divergence from the rough estimate mentioned above, it would be our own impression that estimates of a 50 per cent or higher incidence following benign moles are probably explained by the frequent misinterpretation of certain types of mole as choriocarcinoma, an error which we believe has been avoided in our own study.

Nomenclature

The terms chorioepithelioma and choriocarcinoma have been used interchangeably in the literature to describe the malignant neoplasm arising from the chorionic trophoblast. Of the two the latter would seem preferable, since not a few pathologists speak of benign as well as malignant epitheliomas, while the term carcinoma is accepted by all as indicating a cancer arising from epithelial cells.

The designation of chorioma, suggested by some for the entire group of neoplastic trophoblastic lesions, has attained only a limited degree of usage. If the division into a benign and a malignant group could be sharply made, the division into a chorioma benignum and a chorioma malignum group would seem a sensible one, as suggested by one of us[3] in a previous paper. Un-

fortunately, such a sharp division is impossible, and we must take cognizance of an intermediate group to which a variety of terms has been applied, viz., malignant mole, penetrative mole, invasive mole, and chorioadenoma destruens.

Fig. 1.

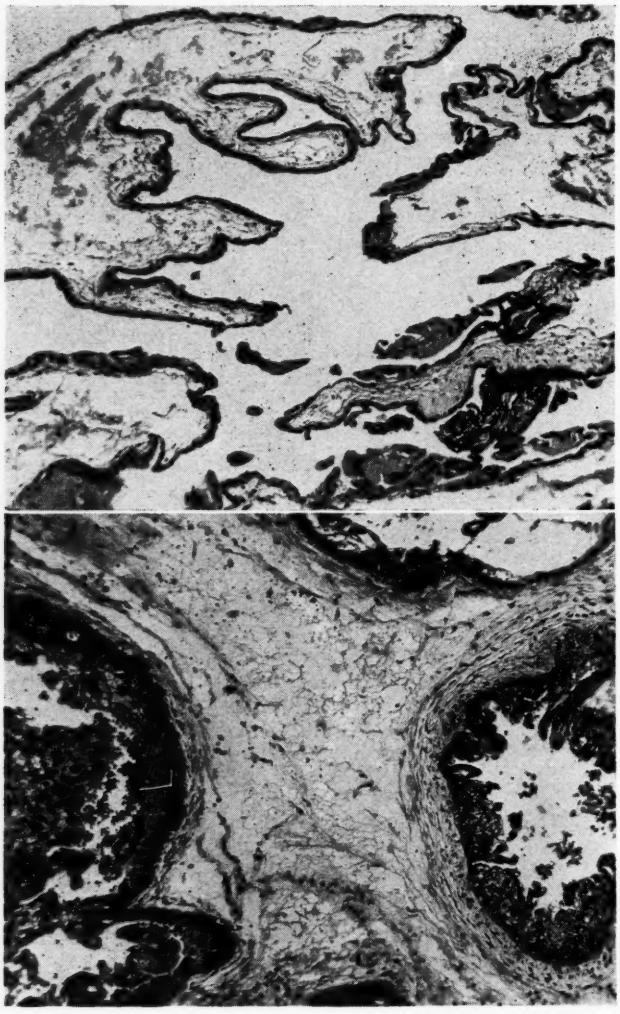

Fig. 2.

Fig. 1 (C.R. 116).—Benign hydatidiform mole, with practically no trophoblastic overgrowth shown in this section of extruded molar tissue. Compare with Fig. 2, showing same mole in situ in uterus.

Fig. 2 (C.R. 116).—Marked trophoblastic overgrowth on surface of large hydropic residual villus (large clear central area) in same mole as shown in Fig. 1. This emphasizes unreliability of trying to evaluate character of mole on basis of extruded or evacuated material.

It is scarcely necessary to point out the inadequacies of and the objections to the first three of these designations, while the fourth, coined by Ewing[4] in 1910, has impressed us as being a very poorly selected one for reasons discussed in the previous publication alluded to. The fact remains, however, that it has attained wide acceptance. For this reason, and because

at this stage of our knowledge no one can suggest a precise term for a group which clinically and pathologically presents considerable variation, it seems wiser to retain the designation of chorioadenoma destruens for this intermediate group.

Curiously enough, its pathologic characteristics have never been clearly defined, either by Ewing himself or by subsequent writers. Since we shall have to include at least some discussion of this troublesome group in the present paper, we have chosen to apply it to two types of hydatidiform mole, as follows:

Fig. 3 (C.R. 115).—Chorioadenoma destruens of penetrative type, which had produced severe intra-abdominal hemorrhage. No trophoblastic overgrowth is seen in the rather degenerated villi found in the removed uterus, though patient had previously passed a typical hydatidiform mole.

1. The first includes those showing an inordinate degree of the trophoblastic proliferation which is a distinctive and, in the minds of many, the most distinctive feature of all moles, especially as they exist in situ in the uterus. It is obvious that this criterion has only limited value in the interpretation of molar tissue evacuated from the uterine cavity, since such molar tissue, being degenerated because of its separation from the nutrient uterine walls, so often shows a far lesser degree of the trophoblastic overgrowth revealed by the same mole in situ.

Another clear disadvantage of utilizing the degree of trophoblastic overgrowth as a guide to classification is that it at once introduces the subjective factor in the appraisal of the degree of trophoblastic overgrowth. However, when large fields of trophoblastic tissue are revealed, together with a well-preserved villous pattern, it would seem justified to conclude that the malignant potentialities of the lesion might be much greater than in the moderate trophoblastic proliferation characterizing the far more common benign moles.

It will be seen that stress has been placed upon the presence of villi, and, as has been emphasized by one of us in a previous paper, the presence of villi should make one lean away from the diagnosis of choriocarcinoma, regardless of the degree of trophoblastic overgrowth. This is certainly not an original observation, for the same point has been emphasized by Meyer and others. Nor can the statement be made without qualification, as is illustrated by at least one of our cases, and as will be further discussed later in this paper.

Fig. 4 (C.R. 80).—Vaginal nodule in a case of chorioadenoma destruens, showing villus with marked trophoblastic overgrowth. Patient has remained entirely well for more than 4 years following hysterectomy.

2. The second criterion for the application of the term chorioadenoma destruens, as we have employed it, is undue penetration of the mole through the uterine wall into the peritoneal cavity, the parametrium, or vaginal vault. Since all moles are more or less invasive, this definition might again seem to introduce the subjective factor, but, as a matter of fact, such local invasiveness is likely to manifest itself objectively by such clinical manifestations as intraperitoneal bleeding, palpable parametrial invasion, or palpable or visible vaginal extension. In spite of the local invasiveness of such moles, there is little tendency to distant metastasis, though exceptions occasionally occur, as in some of our own cases (Cases C.R. 65, 70, 196, 202, 213, 270). It is of interest that the term chorioadenoma destruens was coined by Ewing to indicate the relatively good prognosis in just this group of locally invasive but not metastasizing moles.

As for the benign choriomas, the ordinary benign hydatidiform moles, it is scarcely necessary to review their microscopic characteristics, as these are familiar to most pathologists, viz., the varying but usually moderate degree of

trophoblastic proliferation, the stromal edema and the absence or extreme scantiness of stromal blood vessels. The fact that so many pathologists have such infrequent opportunities to familiarize themselves with the whole trophoblastic group of lesions no doubt explains the very great frequency with which moles which are histologically entirely benign are diagnosed as chorionepithelioma, as shown in Table IV. In a previous paper, one of us (E. N.)[5] has emphasized the fallacy and hazard of attempting to evaluate or grade degrees of clinical malignancy by the examination of evacuated molar tissue according to the plan proposed by Hertig and Sheldon.[6] The more recent studies of Hunt, Dockerty, and Randall,[7] based on a comparatively small material, also cast much doubt upon the value of the scheme of histologic classification of evacuated molar material suggested by Hertig and Sheldon, though very much the same objection can be made to the three groups which are described by the Mayo Clinic group, as well as to the similar grouping of Grady.[8]

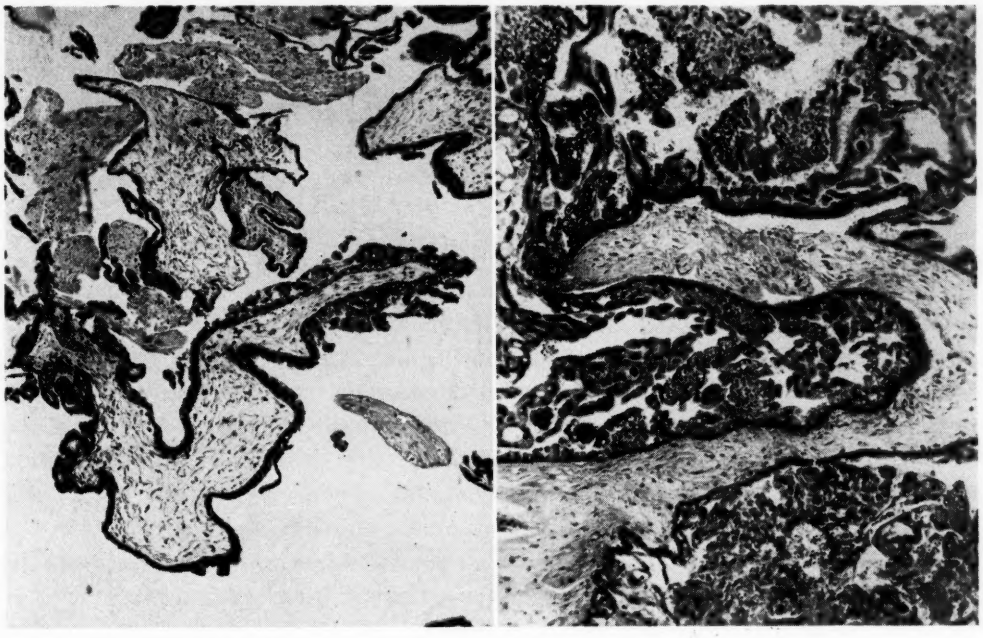

Fig. 5. Fig. 6.

Fig. 5 (C.R. 202).—Benign mole, showing only very slight trophoblastic proliferation.
Fig. 6 (C.R. 202).—The same mole, as seen in the removed uterus, showing very marked trophoblastic overgrowth (chorioadenoma destruens).

Material

It is believed that the rapidly growing Mathieu Memorial Chorionepithelioma Registry already contains a larger number of authenticated choriocarcinomas than have been previously available for study by any one pathologist or group of pathologists. The present study is based entirely on the 74 cases of choriocarcinoma in this collection. The superiority of such a material for purposes of pathologic study and classification over the numerous collective studies based on reported cases has already been stressed. This is rather

glaringly exemplified by the paper of Mathieu,[9] published in 1939 and based simply on the diagnoses of local hospital pathologists in a large number of the Pacific states, with no effort to confirm such diagnoses, or, for that matter, to include any pathologic studies at all. The fact that only 5 per cent of the patients with diagnoses of choriocarcinoma died is proof enough of the worthlessness of conclusions based on such studies.

The recent paper of Park and Lees[10] is another example of the fallacy of basing diagnoses and statistics on cases gleaned from the literature. Of the 516 cases thus collected only 28 were available for personal study, with practically no discussion of the pathologic findings and not a single photomicrograph. It is the pathologic examination which makes the diagnosis of this lesion, and not the clinical history or the hormonal findings. In spite of the excellent academic discussions included in this paper, it serves only to confuse the reader, especially since the authors seem to use the terms chorioma and choriocarcinoma interchangeably. A glance at the tabulation of their 28 cases makes it quite evident that a large proportion of them are not choriocarcinomas at all.

It is the pathologic study of choriocarcinoma and its pathologic differentiation from benign trophoblastic lesions which is so richly available in our own material, and which will therefore be accented in the present paper.

Pathology

Microscopic.—In view of the high incidence of error in the microscopic diagnosis of choriocarcinoma it should be borne in mind that the largest number of the mistakes are made in designating as choriocarcinoma lesions which are actually benign moles with varying degrees of trophoblastic proliferation or those which should be properly designated as chorioadenoma destruens, and not vice versa. To put it another way, it is the false positives and not the false negatives which have confused and vitiated the whole literature of the subject. The frankly malignant choriocarcinoma can rarely be mistaken for anything else, this statement referring of course to examination of the removed uterus and not to examination of curettings, as will be discussed later.

The presence of large fields of trophoblastic cells, with varying proportions between the syncytial and Langhans elements, throughout the uterine wall, with no sign of a villous pattern, and with adjoining areas of hemorrhage and necrosis, leaves little doubt as to the diagnosis. It will be noted that stress has been put on the absence of villi and nothing has been said of anaplastic activity of the tumor cells, and this has been our own reaction in the study of our large material. On the first point, we still feel, as has been stated in a previous paper, that the finding of well-formed villi, even though there is exuberant trophoblastic overgrowth, should always make one lean away from the diagnosis of choriocarcinoma. This is not a new observation, for it has been made by previous writers, like Robert Meyer, who have had the opportunity of studying many cases. It would be wrong to say that villi are never seen in a choriocarcinomatous lesion, but the fact remains that in only one of

our 74 cases (C. R. 139), a tumor which metastasized and killed the patient, were a few villi demonstrable (Fig. 7). Theoretically, there appears to be no reason why one might not occasionally find vestiges of the villi from whose trophoblastic covering the tumor has arisen, but the occurrence is rare in our own experience and apparently in that of others.

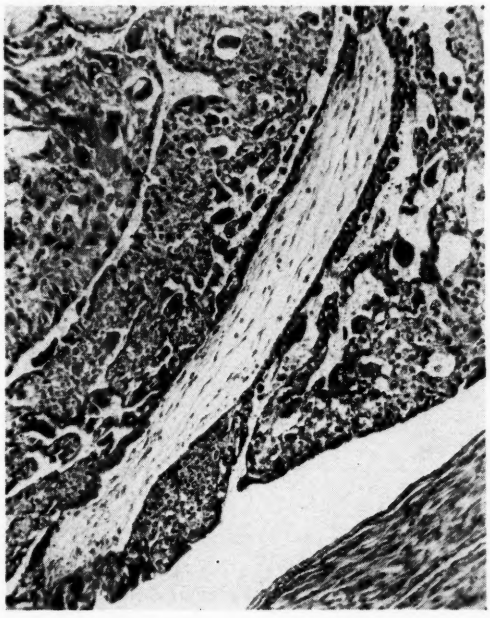

Fig. 7 (C.R. 139).—Choriocarcinoma with widespread dissemination and death. The microscopic picture is entirely characteristic except that a few villi are found (see illustration), this being the only instance of this sort in all our 74 cases.

On the second point, that of the frequently emphasized anaplastic activity of the tumor cells, we are frank to say that we have found this criterion of little value in microscopic diagnosis. It is in the Langhans cells rather than in syncytium that one would look for evidences of anaplastic activity, and yet in quite a number of our choriocarcinomas which metastasized and killed the patients the cytotrophoblastic cells were remarkably mature and well differentiated, with no mitoses and no hyperchromatosis. By contrast it should be remembered that mitoses are not at all rare in normal young trophoblast. Again, one must remember that such nuclear degenerative changes as karyorrhexis and pyknosis may easily be mistaken for mitoses. In some tumors of course there is obvious evidence of anaplasia in the form of mitoses, sometimes numerous, but on the whole we are frank to say that the general pattern and architecture of choriocarcinoma have seemed to us far more valuable diagnostic aids than a study of the individual cells.

In the great majority of these tumors both types of trophoblastic elements have mingled in fairly comparable proportions, though, in some tumors, one type clearly dominates over the other. In Case C.R. 86, for example, the great preponderance of Langhans cells is clearly evident (Fig. 8). The statement is sometimes made that tumors showing such a preponderance of Lang-

hans cells are likely to be of an especially high degree of malignancy, but we have not been able to verify this, possibly because the number of such cases in our own material is too small. It is generally agreed that the syncytium is a derivative of the cytotrophoblast, and this might indicate a higher degree of unripeness in the Langhans elements, but the intermingling of both types in the overwhelming majority of cases makes it impossible to appraise separately the potentialities of the two cell types.

As bearing on this point, mention may be made of the so-called syncytioma described by Marchand as far back as 1895, and designated by him as a variety of atypical chorionepithelioma. We ourselves have never seen a choriocarcinoma made up only of syncytial elements, nor, to our knowledge, has anyone reported a definite neoplasm of this variety, though in an occasional choriocarcinoma a disproportionately large amount of syncytium is seen.

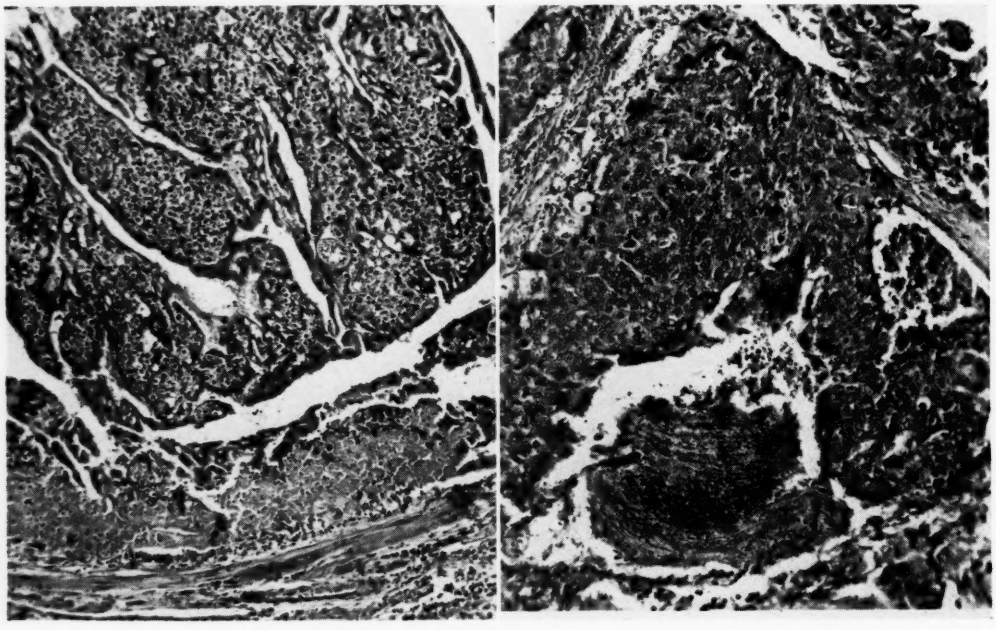

Fig. 8. Fig. 9.

Fig. 8 (C.R. 86).—Choriocarcinoma showing no evidence of anaplastic activity, but with death 11 months after hysterectomy. Compare with Fig. 9.

Fig. 9 (C.R. 93).—Choriocarcinoma with considerable anaplastic activity, but patient has remained well since hysterectomy 4 years ago. Compare with Fig. 8.

There is increasing agreement that the syncytioma spoken of by Marchand is not neoplastic, but that it represents a residuum of trophoblastic cells after either normal pregnancy or hydatidiform mole. The endometrium or decidua often shows such trophoblastic infiltration, and frequently this migration of trophoblastic cells extends deeply into the myometrium, especially in the implantation area. In the endometrium this trophoblastic infiltration is always associated with an inflammatory reaction, so that the common designation of

syncytial endometritis or deciduitis is justified. In the myometrium inflammation is less commonly associated, but the infiltration of the cells between the muscles is characteristically in small clumps or narrow columns (cytotypic, Meyer) with no necrosis of the surrounding muscle, so that one familiar with the process is not likely to confuse it with the bulky masses of trophoblastic cells which invade the musculature in choriocarcinoma, with usually considerable hemorrhage and necrosis.

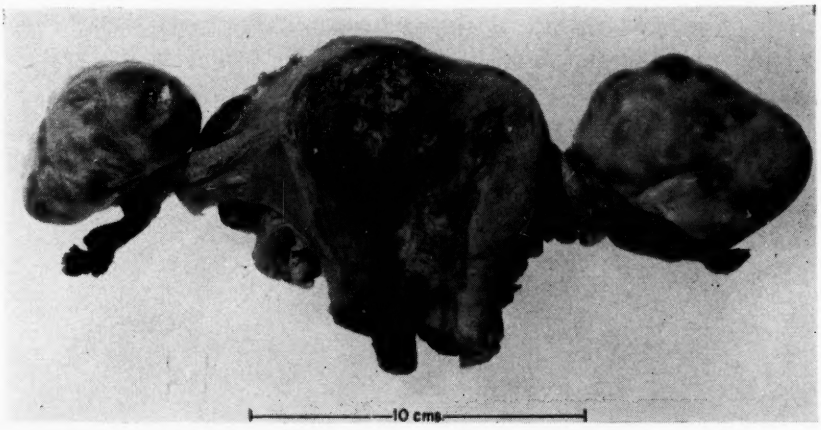

Fig. 10 (C.R. 41).—Gross appearance of rather advanced choriocarcinoma, with death from multiple metastases 1 month after hysterectomy. Note bilateral multiple lutein cysts of ovaries.

Fig. 11 (C.R. 95).—Gross appearance of uterus with small trophoblastic nodule, microscopically choriocarcinoma (see Fig. 12).

The reason for describing this non-neoplastic lesion here lies in the fact that in a surprisingly large proportion of cases it is wrongly diagnosed as choriocarcinoma. No less than 19 of our cases of this non-neoplastic lesion had been thus incorrectly interpreted as choriocarcinoma.

An occasional case of choriocarcinoma may present areas of atypical pattern. In Case C.R. 89 the cytotrophoblastic areas showed a very compact, almost sarcoma-like picture, though other areas were typically choriocarcinomatous. This brings up the still confused question as to the exact histogenetic relation between the maternal decidual cells and the trophoblast and the possible origin of trophoblastic cells from the maternal elements, a question we shall not embark upon, as we have nothing to contribute on this point.

In one of our cases, C.R. 228, the pattern of the tumor is rather curiously gyriform in some areas, though otherwise the lesion is a typical choriocarcinoma.

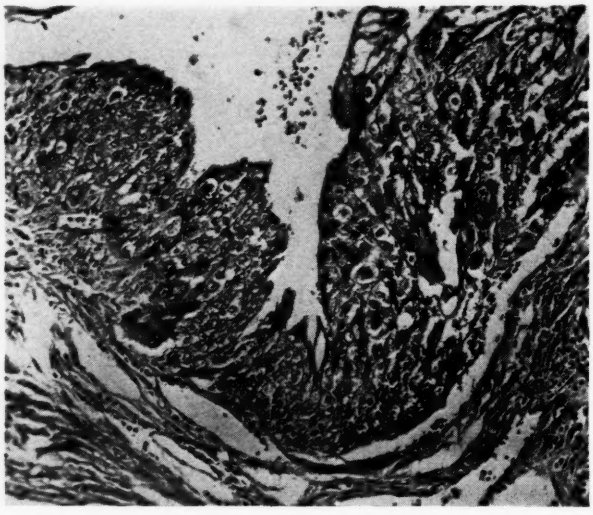

Fig. 12 (C.R. 95).—Choriocarcinoma in uterus shown in Fig. 11. Two previous curettings, with continuing positive hormone tests.

Gross.—While the gross appearance of a choriocarcinoma is fairly characteristic, it is not so absolutely typical as to make a naked-eye diagnosis always possible. To one familiar with the clinical history, especially if this includes knowledge of metastases or the death of the patient, there will be no doubt as to the choriocarcinomatous nature of an extensive grumous, hemorrhagic, or liverlike lesion which may be found in the uterus. On the other hand, the lesion in the uterus may be comparatively small even in the patient who has gone on rapidly to death from extensive metastases. For that matter, the primary lesion may have undergone complete regression even though widespread metastases have brought death to the patient, as we shall presently discuss. In other words, the extent of the primary lesion in the uterus is not by any means an index of the clinical stage of the disease. The so-called trophoblastic nodules in the uterine wall which some have stressed are not by any means characteristic of choriocarcinoma, for similarly hemorrhagic nodules, either single or multiple, are often seen as residua of benign moles. Fig. 11, for example, shows only a small hemorrhagic nodule in the uterine

wall of a patient with choriocarcinoma. For comparison, Fig. 13 shows a similarly hemorrhagic lesion, but much more extensive, in the uterine wall of a patient with residual but entirely benign molar tissue. Even a simple placental polyp may present as a grumous liverlike mass on the interior of the uterus, producing a good simulation of choriocarcinoma. One of us recalls seeing just such a case presented before a medical organization as a choriocarcinoma following full-term delivery, but, when the microscopic slides were thrown on the lantern, the numerous degenerated shadow villi embedded in blood indicated that the lesion was an ordinary placental polyp.

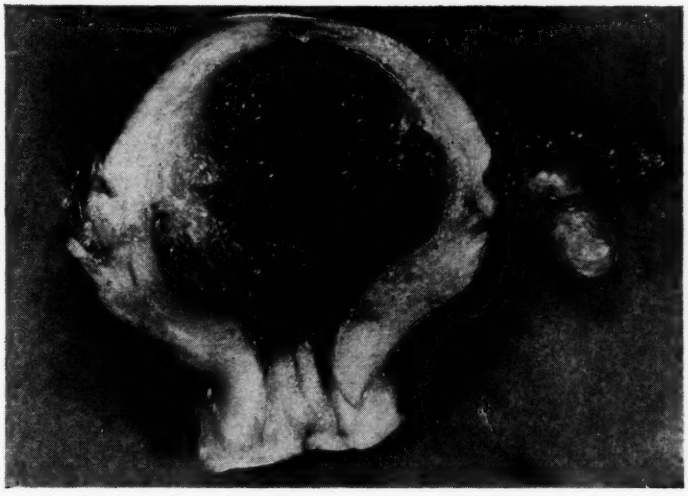

Fig. 13 (C.R. 203).—Uterus containing mass of coagulated blood and a few small vesicles. Choriocarcinoma was suspected, but microscope showed benign hydatidiform mole and syncytial endometritis. Patient living and well nearly 2 years after hysterectomy.

Criteria of Pathologic Diagnosis of Choriocarcinoma

To summarize what has already been said as to the pathologic characteristics of choriocarcinoma, the microscopic diagnosis is based upon the presence of large islands or fields of trophoblastic cells, usually a mingling of both syncytial and Langhans elements in various proportions, and rather characteristically associated with necrosis of the invaded muscle, though this may not be evident in all fields. Hemorrhage is a common finding, as is leukocytic infiltration of varying degree. Anaplastic changes, usually in the form of mitoses and hyperchromatosis, are often found, but are not infrequently absent even in very malignant tumors. We agree with Meyer that there is often no demonstrable difference in the cell characteristics of benign and malignant trophoblast.

There is one other feature which we believe merits re-emphasis. We firmly believe, as we have already stated, that the finding of well-formed villi justifies one in at least leaning away from the diagnosis of choriocarcinoma. On the other hand, to make sure that we are not misunderstood on this point, we do not believe that the occasional finding of villi excludes the diagnosis of choriocarcinoma. With full appreciation of the fact that difficulties are en-

countered in at least a small proportion of cases, we believe that these criteria are sound, and that they are a proper yardstick for the microscopic diagnosis of choriocarcinoma.

Lesions Wrongly Diagnosed as Choriocarcinoma

This one heading alone would furnish the text for a long discussion on the pitfalls of microscopic examination and the high incidence of error. The Registry offers eloquent testimony to the great frequency of false positives in this respect, and the same statement can be made of the literature in general. In no less than 85 cases which had been sent to the Registry with a diagnosis of choriocarcinoma, the lesion was found to be histologically entirely benign. These cases are summarized in Table IV.

TABLE IV. CASES WRONGLY DIAGNOSED AS CHORIOCARCINOMA

Benign mole	46
Syncytial endometritis	19
Chorioadenoma destruens	15
Abortion	3
Normal young decidua of early ovum	1
Degenerating tissue (no trophoblast)	1
Total	85

It will be seen that the 3 lesions most commonly incorrectly diagnosed as choriocarcinoma are benign hydatidiform mole (46 instances), the so-called syncytial endometritis (19 instances), and chorioadenoma destruens (15 instances). It is of interest to note that while our Registry contains 74 instances of what we consider unquestioned choriocarcinoma, fully 85 additional cases sent in with that diagnosis were classified as benign. This appears at once to establish the value of the Registry's most important function, that of authentication and classification of submitted material. We have no doubt that a considerable number of the 85 cases eliminated might otherwise have been erroneously reported as choriocarcinoma, thus adding to the existing vitiation of the literature as regards choriocarcinoma.

Point at Which Definite Diagnosis Can Be Made

We were interested in determining the point in the clinical course of the disease at which the diagnosis of choriocarcinoma was made possible, and our findings are summarized in Table V. In a surprisingly large group, 13 patients, the correct diagnosis was at least strongly indicated by examination of the uterine curettings. It would be foolish to say that such diagnoses could be considered positive, but in all these patients the appearance of the curettings was so very strongly suspicious as to point the way clearly to hysterectomy, and in all these the latter yielded a verification of the diagnosis. On the other hand, and as we have already discussed, it would be completely unjustified to make such a tentative diagnosis on the mere basis of even large localized areas of exuberant trophoblast in the presence of well-formed villi, as such areas are not infrequent in either chorioadenoma destruens or clinically entirely benign moles, as shown in Fig. 15.

TABLE V. POINT AT WHICH A DEFINITE DIAGNOSIS MAY BE MADE

From curettings	13
From hysterectomy	32
From biopsy of metastasis	6
From autopsy	14
Not determinable	9
Total	74

In the largest number of cases, 32, as will be seen from Table V, the diagnosis was established only by examination of the removed uterus, and in 14 only at the time of autopsy. Most of the last-named group represented patients who came under observation in such advanced stages as to preclude operation.

Fig. 14 (C.R. 150).—Curettings from a case of choriocarcinoma, which terminated fatally 5 months later, with multiple metastases.

Finally, an additional word as to the much-discussed question concerning the possibility of diagnosing choriocarcinoma from curettings. In the case of intramural choriocarcinoma, diagnosis from curettings would scarcely be possible, although in the more advanced stages a primary intramural growth can penetrate into the cavity, making it accessible to the curette. When curettage yields large masses of trophoblastic tissue, often anaplastic, with no trace of villous structure, there is little likelihood of error in diagnosing choriocarcinoma. Just such a picture was yielded by curettage in 13 of our cases, and in every one of these cases the diagnosis was confirmed by later examination of the removed uterus. At the other extreme, one need have little concern if the curetted material shows the benign or degenerated villi which are to be

expected after abortion or miscarriage, or the large hydropic villi, with or without trophoblastic overgrowth, which one finds in cases of hydatidiform mole.

We have already spoken of our skepticism concerning the grading of moles according to their supposed malignant potentiality. Even chorioadenoma destruens cannot usually be definitely diagnosed before hysterectomy, certainly not in the locally penetrative variety in which there is little or no trophoblastic proliferation.

On the other hand, in certain cases of chorioadenoma destruens the curettings show large fields of trophoblast which may appear separate and distinct from villi, though their continuity with the latter would be evident if numerous sections were made. Such a suspicious area might easily be misinterpreted as choriocarcinoma (Fig. 15) though the presence in the vicinity of numerous villi should inhibit such a suspicion and induce one to the suspicion of the less deadly chorioadenoma instead.

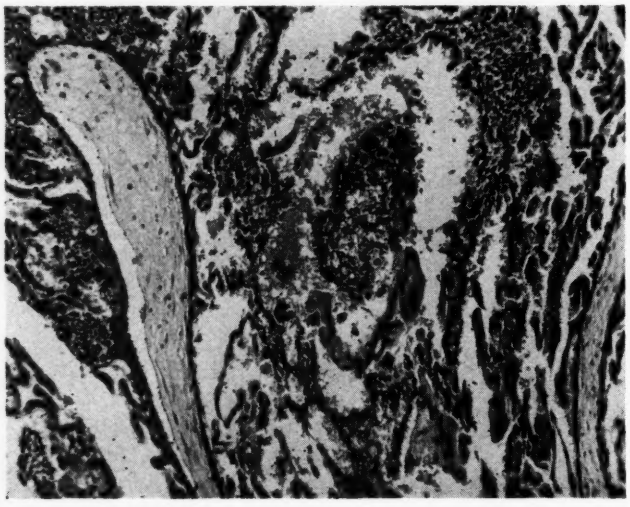

Fig. 15 (C.R. 88).—Chorioadenoma destruens with good villous pattern, but exuberant trophoblastic overgrowth. Sections through latter might simulate choriocarcinoma. Patient living and well 3 years after hysterectomy.

On the whole, therefore, we agree that diagnosis from curettings is rather hazardous, but feel that it can be made with reasonable precision in a minority of cases (13 of our 74 cases).

Metastasis of Choriocarcinoma

The common route of dissemination of choriocarcinoma is unquestionably by way of the blood stream. This would be suggested by the pulmonary deportation of trophoblastic tissue in normal pregnancy itself, and no other explanation seems possible in view of the common location of the metastases. In this respect, this tumor disseminates as does a sarcoma and not as a carcinoma, in spite of the fact that so many of its other pathologic characteristics are carcinoma-like rather than sarcoma-like. In certain metastatic sites, like

the vagina, direct infiltration as well as local vascular and lymphatic permeation must also be invoked, and certainly these are the important factors in the local invasiveness of chorioadenoma destruens.

TABLE VI. METASTATIC SITES

Lung	41
Vagina	12
Brain	11
Liver	7
Kidney	5
Diffuse pelvic metastases	5
Bladder	3
Spleen, pancreas, omentum, broad ligament, ovary, generalized metastases	2
Urethral meatus, mandible, ribs, adrenal gland, hip, stomach, pelvic bones, retroperitoneal implants	1

The acceptance of the prime importance of the hematogenous route in the extension of choriocarcinoma has had some bearing on concepts of treatment. For example, after complete removal of the pelvic organs, there seems to be no rationale for postoperative irradiation of the pelvic field, since the patient is far more likely to die of metastasis to some distant organ like the lungs or brain, than to the pelvic lymph nodes, as in carcinoma of the cervix.

Again, this generally accepted hematogenous concept has led some to advocate conservation of one or both ovaries when hysterectomy is done for choriocarcinoma, especially since metastases to the ovary are relatively rare. That this practice may be hazardous is suggested by an observation in a recent personal case of one of us. In this patient, aged 18, the diagnosis had been previously established by the microscopic examination of the curettings, with strong support by the hormonal findings, the serum gonadotrophic titers being as high as 1,584,000 units per liter. Several x-ray studies of the chest had shown no evidence of lung metastases.

The laparotomy showed the right adnexa to be grossly entirely normal, but the left ovary showed a cystic enlargement the size of a lemon, this being thought to be of the mutliple lutein cystic character so often found with either choriocarcinoma or benign mole. As the patient was only 18, the normal right ovary was retained. However, the later microscopic studies showed the left ovary to be riddled with choriocarcinoma metastasis. It might be added that a repetition of the serum gonadotrophic titer showed the level still to be very high, 564,500 units, so that it was not surprising that several weeks later definite pulmonary metastasis was demonstrable by x-ray, with death of the patient soon afterward.

While conservation of the ovary in this case quite surely played no part in the fatal termination, the observation is of interest in showing that, while the sequence is unusual, extensive metastasis to the ovary can at times antedate the far more frequent metastasis to the lungs.

Metastasis to the Lungs.—This subject has been a very confusing one to us, as it undoubtedly has been to others. X-ray study of the chest has properly

come to be a routine procedure in the investigation of all suspicious cases, and the finding of x-ray evidence of metastasis has been properly interpreted as of ominous significance. The roentgenologists themselves are quick enough to acknowledge possible errors in interpretation. However, the fact that only 2 of our patients in whom pulmonary metastasis had been diagnosed have thus far survived, though for too short periods to justify considering them as cured, speaks for the usual correctness of the x-ray diagnosis, and the usually grave prognostic import. One of these 2 patients (C.R. 220) is living 11 months after hysterectomy, which can be considered definitely hopeful since the overwhelming majority of our patients have not survived beyond 6 months. In the other patient with lung metastasis (C.R. 233) only 4 months has elapsed since operation, so that the outlook must still be considered very uncertain.

On the other side of the question, what about the cases in which the x-ray has apparently shown definite pulmonary involvement in patients in whom the pathologic study of the uterus showed, not choriocarcinoma, but chorioadenoma destruens or even benign hydatidiform mole? To show that the diagnosis was pathologically correct, of the 34 patients in whom the diagnosis of chorioadenoma destruens was made, an adequate follow-up was possible in 26 cases, and all these patients have remained well except for 6, as detailed in Table VII.

TABLE VII. FOLLOW-UP OF CHORIOADENOMA DESTRUENS CASES

NO. OF CASES	DEAD	STILL ALIVE AFTER		NO FOLLOW-UP
		1 YEAR	2 YEARS	
34	6	2	18	8

Cause of Death in the 6 Fatal Cases.—

Two were immediate postoperative deaths (C.R. 102, 157).
C.R. 10 died of internal hemorrhage due to uterine perforation by the tumor.
C.R. 97 died of uremia following a North American operation.
C.R. 196 died of sepsis and repeated hemorrhage from the vaginal metastases.
C.R. 202 died of a spinal lesion which developed one month after hysterectomy. This may or may not be a chorioadenoma destruens metastasis as no postmortem was performed.

It will be seen that in 2 of these cases (C.R. 102 and C.R. 157) the deaths were operative, and in 2 death was due to hemorrhage, either abdominal or vaginal. The remaining 2 are of very great interest and deserve special comment. One of these (C.R. 97) had ben seen by one of us (E. N.) in consultation with Dr. Charles Mazer of Philadelphia. Following the evacuation of a histologically benign mole 2 months previously, she had developed a parametrial mass, and it was thought that she had a locally invasive mole or chorioadenoma destruens which would probably be cured by hysterectomy. However, she was seen shortly afterward by a surgeon who, for some curious reason, promptly performed a partial pelvic exenteration (North American operation), a procedure which seems to us to have been most unwise and illogical in view of the trophoblastic nature of the lesion and its well-known characteristics of dissemination. Death occurred within 2 weeks from pyelonephritis and uremia.

Equally interesting is C.R. 202, in whom a spinal lesion, thought to be metastatic, had developed 1 month after hysterectomy. The lesion had been diagnosed from the curettings as a benign mole, though the classification was changed to chorioadenoma destruens after examination of the uterus (Figs. 5 and 6). Unfortunately, the subsequent data are incomplete, except for the

Fig. 16.

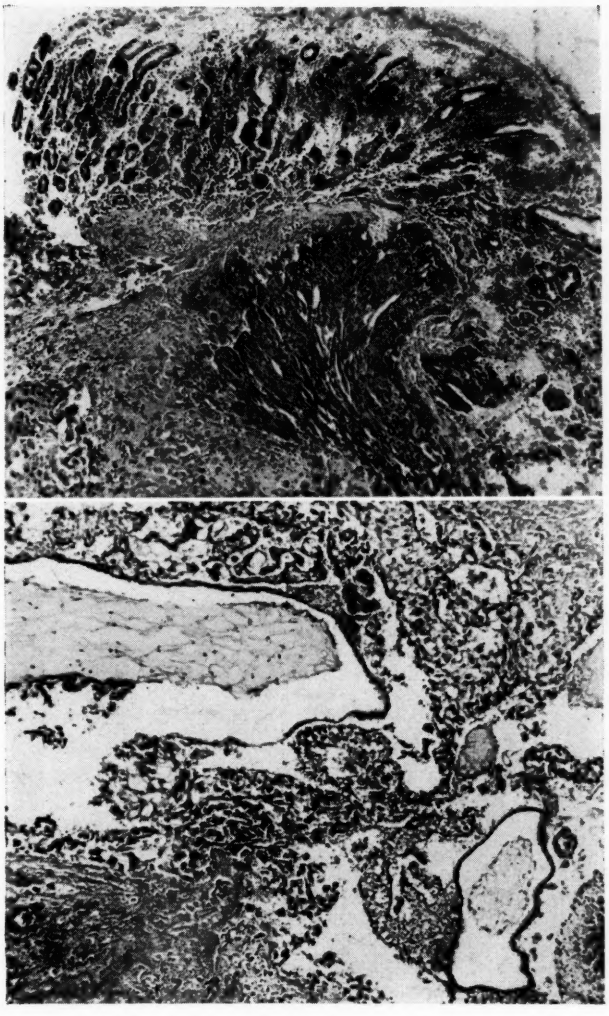

Fig. 17.

Fig. 16 (C.R. 225).—Choriocarcinoma metastasis in wall of stomach, a rare site, though autopsy showed widespread dissemination.

Fig. 17 (C.R. 48).—Villi in pulmonary metastasis of fatal case of choriocarcinoma, though no villi were found in primary uterine lesion.

fact that she later died and no autopsy was obtainable. This case is emphasized, however, because we believe it demonstrates the possibility of pulmonary metastasis with chorioadenoma destruens, or, for that matter, with even benign hydatidiform mole. On the latter point we shall not elaborate,

reserving this for our later study of hydatidiform moles. To illustrate, however, we may refer briefly to a case which will be later reported by Dr. Eleanor Delfs, which she has permitted us to mention. It concerns a patient, who, following evacuation of a histologically benign mole, developed a lung lesion for which a lobectomy was later done. This lesion, on histologic examination, showed again a benign hydatidiform mole. Still later, a spinal-cord lesion developed, which was only incompletely removable, but which again showed benign molar tissue. There was a continuing high gonadotrophic titer, and death followed some months later.

An almost exactly similar instance of pulmonary and spinal metastasis with benign mole, with death 1 month after hysterectomy, and again no autopsy, is represented by our Case C.R. 113. By contrast C.R. 31 is living and well 8 years after hysterectomy for histologically benign mole, although the x-ray had shown a metastatic lesion of the right lower lobe, for which x-ray therapy was used, with complete disappearance of the lesion. Again, C.R. 65 is living and well 4 years after benign mole, associated with metastatic nodules in both lungs, with later spontaneous regression. Still another but probably not unimpeachable case (C.R. 154) is one in which the only section we have available is one of the evacuated uterine material. This shows a histologically benign mole, although the patient is said to have later developed a vaginal metastasis, and also showed x-ray evidence of metastases to the lungs and femur. One cannot exclude the possibility of later choriocarcinoma in the uterus, but this seems unlikely since the patient was still living more than 4 years later (November, 1952).

If normal trophoblastic tissue can be deported to the lungs, there certainly seems to be no reason why similar dissemination cannot occur with either chorioadenoma destruens or benign moles, and there is no longer any doubt as to this possibility. All sorts of vagaries may be encountered. For example, in one of our cases of choriocarcinoma, the uterine lesion showed no villi, but the pulmonary lesion did (C.R. 48) (Fig. 17).

A good many other instances of the peculiarities of behavior of the lung lesions associated with both malignant and benign trophoblastic lesions are to be found in the literature. In the present state of our knowledge, they seem unexplainable except by including biologic considerations in the explanation of the varying degrees of clinical malignancy in tumors which histologically may be exactly the same. It is our own belief that for the present we cannot escape the assumption of a maternal defensive mechanism of varying degrees, both uterine and systemic, against the inroads of a tissue which normally is invasive. However, we shall not here again belabor this hypothesis, as we have no further evidence for it beyond what was presented in a previous publication. In the latter we also raised the possibility that some of the peculiarities of behavior encountered with choriocarcinoma might be linked up with the fact that we are dealing with a tumor of one individual, the fetus, growing in the tissues of another, though closely related individual, the mother,

making it an implantation type of neoplasm. However, the bearing of this fact upon the clinical and pathologic characteristics of choriocarinoma has not been explained.

Disappearance of Primary Uterine Tumor With Death From Metastases

The apparent regression of metastases in the lungs or elsewhere which has been noted by various authors, and of which we have mentioned a number of instances in our Registry material, is perhaps less mystifying than complete disappearance of the original uterine choriocarcinoma, but with death from usually widespread metastases. One might be inclined to doubt this possibility if there were not in the literature a considerable group of such cases which are of unquestioned authenticity. The literature on this point was reviewed in 1930 by Novak and Koff,[11] who reported a convincing case of this sort, with complete autopsy studies. We were rather surprised to find that no less than 7 cases in our present series (C.R. 49, 75, 84, 107, 152, 167, and 178) are of this curious type. All of them died of extensive metastases, although in all of them except C.R. 178 no trace of the uterine lesion could be found. In this last case, only one or two microscopic vestiges of obviously regressing choriocarcinoma could be found, indicating the regression which had occurred in the uterine tumor in this and similar cases (Fig. 18).

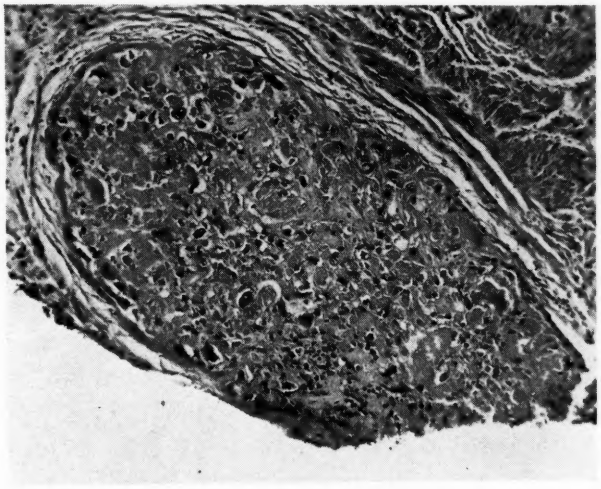

Fig. 18 (C.R. 178).—One or two such regressive trophoblastic nodules as this were only residua of primary choriocarcinoma in uterus, though patient died of extensive metastases.

It would lead us far afield to theorize concerning the spontaneous regression which can undoubtedly occur in either the primary or secondary sites of choriocarcinoma, and this topic has been fully discussed in a recent paper by one of us. Suffice it to say that no explanation suggests itself other than the assumption that there must be both a local and systemic defensive mechanism against the biologic invasiveness of both benign and malignant trophoblast, though thus far we have no knowledge as to the nature or exact source of these defensive factors.

Treatment and Results

There is general agreement that radical removal of the uterus, tubes, and ovaries is the wisest plan of treatment if the condition of the patient warrants such surgery. Unfortunately, the latter condition is not always met, a good many of the patients in our series having presented themselves in such advanced stages that only such inadequate therapy as curettage only, or curettage plus irradiation, or irradiation alone was done. In a good many cases, the preoperative diagnosis was reasonably certain, as in the 13 cases in which microscopic examination of the curettings left little doubt as to the existence of choriocarcinoma. In a large number of cases, 32 of our group, pathologic diagnosis was impossible until after removal of the uterus.

Fig. 19 (C.R. 42).—Residual benign molar tissue deep in uterine wall, the most common cause of persistent positive hormone tests, even after repeated curettage, as in this case. Negative postoperative hormone tests.

This is the situation which so often confronts the clinician in the management of hydatidiform mole. Without going into great detail, the usual plan is evacuation of the mole, followed by hormonal studies, and repetition of the curettage if the biologic tests remain positive for a considerable time, and especially if the patient continues to bleed and the uterus remains subinvoluted. If the biologic tests still continue positive and especially if the titer increases, hysterectomy is accepted as fully justified. In only a small proportion will choriocarcinoma be revealed, the far more common finding being residua of trophoblast, usually including residual hydatidiform villi, deep in the uterine wall and beyond the reach of the curette (Fig. 19).

In other words, to ensure removal of the occasional genuine choriocarcinoma, it is necessary to sacrifice a good many uteri harboring lesions which are not malignant, and which would usually ultimately undergo regression and disappear. However, the possibility that, in at least some of these cases, choriocarcinoma might later develop from trophoblastic residua offers additional justification for hysterectomy in this group. Individual circumstances

may at times warrant departures from this brief résumé of the usual management of hydatidiform mole, but this is not the place for more complete elaboration in a paper dealing primarily with choriocarcinoma. Table VIII summarizes the various plans of treatment in the 74 cases in our series, together with the result.

Survival Rate

On no point has the literature shown such wide divergence as in estimates as to the degree of malignancy of choriocarcinoma. At one extreme one finds the gloomy and much-quoted statement of the late James R. Ewing[12] that he had never seen a patient with choriocarcinoma survive. At the other extreme is the statement of Mathieu that only 5 per cent of such cases end fatally. Both of these estimates are unquestionably wrong, while most of the estimates made by others are clearly open to the criticism of the doubtful authenticity of the reported cases on which they are so often based. It would be of no advantage to quote or analyze the survival rates given by various others.

The final and decisive diagnosis of choriocarcinoma is made by the microscope, and in this respect we feel that our own study can be considered a genuine contribution to this much-discussed question. We confess that we were somewhat surprised by the fact that fully 16 of our 74 patients were living and free of recurrence for periods of 6 months or longer. With other types of malignancy, a follow-up of only 6 months would be absurdly inadequate, but everyone agrees that only a small proportion of patients with choriocarcinoma survive beyond 6 months. There were only 2 survivals of more than a year in our fatal cases. At any rate, we have felt justified in including in our tabulation of survival the 3 patients who had been followed only 6 months. The other 13 survivors have remained well for a number of years, and we do not feel that the follow-up in these cases is inadequate with this rapidly progressing disease. Eliminating the 3 cases with only a 6 months' follow-up, 13 of our 74 patients, or 17.5 per cent, have remained well.

TABLE VIII. TREATMENT AND SURVIVAL

TREATMENT	NO.	DEAD	STILL ALIVE AFTER			
			6 MONTHS	1 YEAR	2 YEARS	NOT FOLLOWED
Hysterectomy	42	23	1	2	10	6
Hysterectomy and pelvic irradiation	6	3	1		1	1
Hysterectomy and chest irradiation	6	4	1			1
Hysterectomy and pulmonary lobectomy	1	1				
Hysterectomy, pulmonary lobectomy, and partial cystectomy	1	1				
Hysterectomy and ligation of inferior vena cava	1	1				
Hysterectomy and excision of cerebral metastasis	1	1				
Hysterectomy and partial gastrectomy	1	1				
Curettage only	6	6				
Curettage and irradiation	1	1				
Irradiation only	1	1				
No treatment	7	7				
Total	74	50	3	2	11	8

The figures given in Table VIII dispose of the cynical statement sometimes heard that if a patient with supposed choriocarcinoma gets well she did not actually have a choriocarcinoma, because the diagnosis in all our cases was made pathologically, with exactly the same criteria in all cases, as previously described. As a matter of fact, in every patient who has survived we have gone back to the original material to see if we could convince ourselves that the lesion might not have been a choriocarcinoma, but in all cases its pathologic characteristics were exactly like those of the larger number of fatal cases.

Duration of Life in Fatal Cases

The 50 fatal cases in our series are tabulated in Table IX, with the duration of life after treatment. It will be seen that in only 2 of the patients in whom this information was obtainable did the patients live more than one year. One of these, C.R. 139, survived 14 months, and the other, C.R. 167, 3 years and 1 month. This patient had had a total left pneumonectomy 20 months after hysterectomy, and 17 months before her death from widespread metastasis. It is of interest that this is one of the patients in whom at the time of hysterectomy no trace of the original uterine lesion could be found.

TABLE IX. FATAL CASES OF CHORIOCARCINOMA

	TOTAL	WITHIN 1 WEEK	WITHIN 1 MONTH	WITHIN 6 MONTHS	WITHIN 1 YEAR	OVER 1 YEAR	NOT KNOWN
After hysterectomy	35	4	4	20	3	2	2
After curettage	6		3	3			
After curettage and irradiation	1			1			
After irradiation only	1		1				
No treatment	7	4	2	1			
Total	50	8	10	25	3	2	2

Of the two patients who survived over one year, one, C.R. 139, lived 14 months (case of choriocarcinoma with villi) and the other, C.R. 167, lived 3 years and 1 month. She had a total left pneumonectomy 20 months after hysterectomy and 17 months before her death from widespread metastases. At hysterectomy no tumor was found in the uterus.

Summary

This study is based on the rich material of the Mathieu Memorial Chorionepithelioma Registry. This includes 74 cases of authenticated choriocarcinoma, probably the largest group ever available for direct study by a single group of pathologists. It is chiefly as regards pathology, pathologic differentiation, dissemination, and prognosis that our material is most helpful, and it is these aspects which are selected for special emphasis in this paper.

The question of nomenclature is discussed, with criteria for the classification we have used. The microscope is the final arbiter of diagnosis, and not the clinical course or the biologic behavior. The routes of dissemination are discussed and tabulated, with discussion of certain vagaries, such as the occurrence of metastasis in the usually only locally invasive chorioadenoma destruens or even benign mole, the possibility of spontaneous therapeutic re-

gression of metastases, or of the primary uterine site with death from metastases, etc. We consider our survival figures more accurate than most others, because we believe all our cases are authentic choriocarcinoma. Of our 74 patients 13 (17.5 per cent) are living without recurrence one year or more, an adequate follow-up period for this rapidly fatal disease, which usually kills within 6 months. If we were to add 3 additional survivors living and well only 6 months, the survival rate would be increased to 21.6 per cent.

References

1. Marchand, F.: Monatschr. f. Geburtsh. u. Gynäk. **1:** 419, 1895; Ztschr. f. Geburtsh. u. Gynäk. **32:** 405, 1895.
2. Meyer, R.: In Henke, F., and Lubarsch, O., editors: Handbuch der speziellen pathologischen Anatomie und Histologie, Band VII, Berlin, 1930, Julius Springer; Ztschr. f. Geburtsh. u. Gynäk. **92:** 259, 1927-1928.
3. Novak, E.: J. A. M. A. **78:** 1771, 1922.
4. Ewing, J. R.: Surg., Gynec. & Obst. **10:** 366, 1910.
5. Novak, E.: Am. J. Obst. & Gynec. **59:** 1355, 1950.
6. Hertig, A. T., and Sheldon, W. H.: Am. J. Obst. & Gynec. **53:** 1, 1947.
7. Hunt, W., Dockerty, M. B., and Randall, L. M.: Obst. & Gynec. **1:** 593, 1953.
8. Grady, H.: Read before Sect. on Path. and Phys., A. M. A., New York, 1953 (not yet published).
9. Mathieu, A.: Am. J. Obst. & Gynec. **37:** 654, 1939; Internat. Abstr. Surg. **68:** 52, 181, 1939.
10. Park, W. W., and Lees, J. C.: Arch. Path. **49:** 73, 205, 1950.
11. Novak, E., and Koff, A. K.: Am. J. Obst. & Gynec. **20:** 153, 1930.
12. Ewing, J. R.: Neoplastic Diseases, ed. 4, Philadelphia, 1941, W. B. Saunders Company.

Discussion

DR. A. N. ARNESON, St. Louis, Mo.—After reading the full text of Dr. Novak's work I have deemed it appropriate to comment upon pulmonary dispersion of choriocarcinoma, and its response to irradiation.

As a basis for discussion, it should be noted that Dr. Novak cites 4 cases of chorioadenoma destruens with pulmonary metastases. One of those to be reported later by Dr. Delfs is said to be growing progressively worse after treatment by lobectomy. Another patient died after 13 months without autopsy. The two remaining patients are living and well after hysterectomy for 4 and 8 years, respectively. Pulmonary lesions regressed spontaneously in one, and after chest irradiation in the other. Dr. Novak also describes two patients with choriocarcinoma showing lung metastases who are living 4 and 11 months following hysterectomy. Chest irradiation was employed in both instances.

Possibility of pulmonary spread of trophoblastic tissue is well established in normal pregnancy, the intermediate group of moles, and in choriocarcinoma. The occurrence of spontaneous regression at metastatic as well as at primary points confounds interpretation of radiation effects in the abnormal forms. Individual experience is limited, and the more malignant tumors frequently result fatally before effects of radiation treatment can be determined. Published reports are almost invariably pessimistic, but many fail to specify the amounts of radiation applied. Mention might be made of the experience reported by Levy in which large doses of pelvic irradiation applied for recognizable tumor in that region were followed by disappearance of pulmonary lesions in 2 patients alive and well for four and seven years, respectively. In 1936 Davis and Brunschwig reported control of pelvic disease with x-rays. Dr. Novak suggests that hematogenous dispersion of choriocarcinoma makes post-hysterectomy pelvic irradiation illogical, because the patient is more likely to die of distant metastases than from local spread. No promise is to be found for chest irradiation, however, a point which holds for lung metastases in all malignant tumors.

Nine patients believed to have choriocarcinoma have been observed in our group. Those patients have been reviewed by Monat, and 5 received chest irradiation for pulmonary metas-

tases. All of these died during the course of treatment, or very promptly thereafter. Haskins and Sherman employed large amounts of androgen, and later estrogen without evidence of tumor effect.

One additional case observed at Brooke General Hospital, Ft. Sam Houston, Texas, should be mentioned. The entire course included a period of about 15 months following passage of a hydatid mole of 4 months' gestation. With persistent symptoms, hysterectomy was performed 2 weeks after expulsion of the mole. Villi were present, but due to anaplasia and invasiveness the lesion was considered to be a malignant mole. The high hormone titer fell gradually with negative values occurring after 10 months' observation, but positive values with increasing titer appeared the following month, and 4 months later a radiograph revealed for the first time the presence of lung metastases. The pelvis had been clinically free of recurrence, and remained so throughout the remaining month of life until proved otherwise at autopsy, but x-ray treatment was applied over that region as well as over the chest. The lungs received 1,400 r (air) through each of 4 fields measuring 10 by 15 cm. Radiographs made during treatment revealed progressive involvement. Symptoms of intracranial pressure developed abruptly, and the patient died from brain hemorrhage. Autopsy showed no evidence of radiation effect upon the pulmonary lesions.

The abrupt change in clinical course, and the absence of histologic evidence of radiation effect creates a sense of futility. Dr. Novak poses the interesting conjecture of tissue resistance acting to produce some of the vagaries of behavior for trophoblastic tumors, and while no attempt is here made to compare choriocarcinoma with anaplastic lesions of adult tissue, there is basis for extending his concept to regression following irradiation. In the preoperative treatment of endometrial cancer the undifferentiated forms are more likely to persist. Anna Goldfeder noted that phenomenon in experimental tumors in animals. Dr. Otto Schwarz repeated many times the supposition that study of choriocarcinoma should be of value in exploring the etiology of cancer. Time will answer that possibility.

DR. HERBERT E. SCHMITZ, Chicago, Ill.—This report has helped to justify the effort and expense assumed by the American Association of Obstetricians, Gynecologists and Abdominal Surgeons incurred by the acceptance of the late Albert Holman's generous offer to create a memorial to his former chief, Albert Mathieu. The success of this Chorionepithelioma Registry in collecting material is, I am sure, in great part due to the industry and ability of its chairman, Emil Novak, whose valued opinion is sought after by the numerous gynecologists and pathologists who have submitted material. As the authors have stated, "It is to be doubted that any one group has ever previously had the opportunity of direct study of such a large material."

The 85 cases wrongly diagnosed as choriocarcinoma, listed in Table IV, demonstrate the need for a uniform nomenclature, as discrepancies in definition of changes which indicate choriocarcinoma, chorioadenoma destruens, syncytial endometritis, invasive mole, and benign mole are frequently confusing and responsible for incorrect diagnoses. The authors' definitions with the attached photomicrographs are clear and should eliminate future reports with glaring discrepanices.

Emphasis must be placed on the observation that the finding of well-formed villi does not justify excluding the diagnosis of choriocarcinoma; the finding of villi has been too generally accepted as proof positive that choriocarcinoma did not exist.

The question as to the exact histogenetic relation between the maternal decidual cells and the trophoblast and the possible origin of trophoblastic cells from the maternal elements is, as the authors state, highly speculative. In a study of extragenital choriocarcinoma, Hirsch concludes, "Trophoblastic tissues are a characteristic of the male germinal tissues (testes) not of the mature female (ovary) and that the male element contributes the trophoblastic tissue component when chorio-carcinoma develops from a fertilized ovum in the uterus or adnexa as a complication of pregnancy." He continues with the statement, "The almost total absence of reports of chorio-carcinoma of the ovary of the adult female supports this view." One might speculate, therefore, that the trophoblastic tissues (placenta) are contributed by the male element in the normal development of a fertilized ovum in the uterus.

That the benignity or malignancy of the trophoblast cannot be determined from the cell characteristics is an important observation which merits support and re-emphasis.

The question of metastasis of choriocarcinoma is of great interest in the light of our present knowledge. Surely, we must review with great suspicion those cases reported as cured by irradiation or spontaneous regression following hysterectomy. Undoubtedly a preponderant number of these cases would be found to be chorioadenoma destruens or benign hydatidiform mole with penetration or pulmonary metastases. Case C.R. 31 is an example of unnecessary irradiation therapy, for spontaneous regression would have occurred as in Case C.R. 65. Suspicious x-ray findings should not deter us from further investigation and therapy, for is it not possible that we may be dealing with choriocarcinoma still confined to the uterus and benign metastases of trophoblastic elements to the lung? I feel sure that future studies will demonstrate that this is possible.

I cannot agree with the authors' optimism over the 17.5 per cent survival, namely, 13 of the 74 patients with a proved diagnosis of choriocarcinoma. Certainly most of these patients succumb within six months but, as the authors stress, there are different degrees of malignancy in all tumors as well as varying degrees of resistance on the part of the host. That some of these patients will yet succumb to the disease seems inevitable.

It is imperative, however, that the often repeated statement to the effect that, if the patient survives, she did not have choriocarcinoma, be deleted from the literature.

The question of improving these survival rates is the concern of all clinicians. When confronted by such a problem, the fact that only 17 per cent of the cases in this series were diagnosed by curettage is of great importance. Delay caused by further hormone titer studies may be costly, yet 66 per cent of these patients are less than 30 years of age and preservation of the uterus and further childbearing most desirable. It seems, therefore, that our dilemma still exists for choriocarcinoma as for all malignant disease, namely, how to diagnose the disease when treatment is most effective. Until additional and more accurate diagnostic procedures are made available, an occasional uterus will have to be sacrificed because the biologic tests continue positive after evacuation of the mole. Procrastination in such an instance will deprive the patient with localized choriocarcinoma of the chance of recovery that early total abdominal hysterectomy and bilateral salpingo-oophorectomy offer her. Preservation of ovarian tissue is not justified by the evidence presented.

The authors are to be complimented for a clear, concise, and practical study of an important disease which has confused the clinician and, as a result, has been badly managed.

DR. THADDEUS L. MONTGOMERY, Philadelphia, Pa.—To those interested in obstetric and gynecologic pathology, hydatidiform mole and chorionepithelioma have always presented intriguing problems. Among the latter, one of the major clinical and histologic considerations is the stage at which the growth of the chorionic ectoderm ceases to be benign and becomes malignant in its propensities.

Hertig, Novak, and others have attacked this problem before, and the paper to which we have just listened, based upon a large number of well-documented cases, is a valiant attempt to solve it.

Unfortunately, there is no universally accepted criterion upon which the diagnosis of malignancy in this peculiar lesion can be based. Send a well-selected specimen of growth, with adjacent tissue, to a number of prominent gynecologic pathologists for opinion, and the replies will be more contradictory than those in many instances of intraepithelial carcinoma of the cervix. Apparently it is still a controversial subject.

Actually what is well known about hydatidiform mole and chorionepithelioma is approximately as follows:

First, in these conditions the chorionic ectoderm flourishes independently of the presence of the embryo and independently of vascular development in the villous stroma. This is quite in contrast to normal pregnancy, where the growth activity decreases during the course of pregnancy and falls away abruptly at term, and transient bits of syncytium are absorbed after the conclusion of pregnancy.

Second, the growth activity and the pathologic propensities of this tissue vary from the stage of mildest hydatidiform mole, to the ravaging growth of the syncytium in choriocarcinoma.

Third, in the case of the milder forms of hydatidiform mole the prompt removal of the bulk of neoplastic tissue will often permit the maternal system to absorb the remnants of ectoderm, and the patient recovers; whereas in the wilder growing specimens the ectodermal activity overwhelms the host, and the biologic resistance that the mother might otherwise rally fails to manifest itself.

Fourth, in any case left to itself, in the instance of either the so-called benign hydatidiform mole or the malignant choriocarcinoma, the chorionic ectoderm creates destruction, be it local or systemic. The adjacent tissue is invaded, vascular channels are disrupted, violent hemorrhage occurs, bits of trophoblast are carried to distal organs, and the function of parenchymatous structures is disrupted. In any case, the patient may succumb if untreated.

In view of these considerations, I think we would be in better case clinically and histologically if we considered all independent growth of the chorion as malignant and classified its activity as we do in many other forms of cancer, as Grade I, Grade II, Grade III, and Grade IV, depending upon the degree of proliferation and anaplasia of the ectoderm, the amount of villous stroma present, and the invasive properties of the tumor as a whole.

By so doing, some of the confusion regarding a relatively false dividing line between "benign" hydatidiform mole, and "malignant" choriocarcinoma might be dispelled, and greater attention called to the real and potential seriousness of all such growths.

DR. HOWARD C. STEARNS, Portland, Ore.—I think it is pertinent to present one other facet of this interesting subject. One of the patients Dr. Novak presented possibly is the one I have in mind for the material sent the Registry. It involved an individual who had a mole the size of a six months' pregnancy, followed by chorionepithelioma or choriocarcinoma, followed by hysterectomy and removal of the tubes and ovaries. Thereafter she developed chest metastases proved by x-ray and titer studies, and we thought she was beyond hope. At the suggestion of Dr. Heller of our endocrinology section at the medical school, stilbestrol was started. With a small dose intramuscularly the titer dropped and the x-ray pictures and the clinical aspects proved that the lesion was on the wane. On such therapy she remained reasonably well for nearly four years. When we stopped the intramuscular injection of stilbestrol and started giving the drug orally, the titer rose and the patient became ill. We went back to the intramuscular administration, and the titer dropped. We could raise or lower the titer by altering the dosage. The patient eventually died four years later of chorionepithelioma or choriocarcinoma. We felt that estrogens definitely prolonged her life.

While I know that not all cases respond so well to this drug, I wonder if some of the so-called chorioadenoma destruens might not be subdued with estrogens, sufficiently perhaps even to prevent a hysterectomy. If we could get a good Christian Scientist who refused operation, perhaps we could find out what might happen. It is my suspicion that local resection of such growths when they are well localized, or treatment with estrogens might stamp them out.

DR. WILLIAM BENBOW THOMPSON, Los Angeles, Calif.—I do not wish to talk about the pathological material that has been displayed, but merely about the finances of the Albert Mathieu Registry. Dr. Schmitz mentioned that this was originated by a gift from the late Dr. Holman. After that gift was expended, the Association met the expenses for a few years until the American Cancer Society made a grant for 1952. These funds, however, were small, and I am sure that a careful audit would establish that the Registry would have gone out of existence except for the generous contributions of materials, time, and money by Dr. Novak and his laboratory staff.

There are four of us at this meeting who are members of the Committee of the Mid-Winter Assembly of Southern California, which now has taken over the financial support of

the Registry as a memorial not only to Albert Mathieu, but also to Dr. Holman, who continued the studies initiated by Dr. Mathieu. It will be pleasing to us to report to our Committee that the Assembly will continue the sponsorship of the Registry, and I think I may assure the Association that never again will the Association have to use its funds for the Registry.

DR. NOVAK (Closing).—To start with the last comment on my paper, I am frank to say that Dr. Montgomery's suggestion of calling all of this group of trophoblastic lesions chorionepithelioma and then trying to grade them does not appeal to me at all. I suppose that with such a plan we'd have to start with the normal trophoblast as a sort of Stage 0, and we'd be including both benign and malignant lesions in such a gradation. Such a scheme would seem to be a very defeatist one, since I believe that our study has shown that the benign or malignant nature of trophoblastic lesions can be determined by the microscope in the great majority of cases.

Dr. Schmitz is perfectly right in saying that recurrence may at times occur after the one-year follow-up period which we employed, but, as a matter of fact, survival for more than one year occurred in only 2 of our fatal cases, a proportion much less than that of carcinomas of the cervix recurring after the customary five-year follow-up period.

Our comments on therapy were based on a purely factual report of that used in the cases included in this report, so that we did not feel called upon to discuss the hormone plans which have been tried in a very small number of reported cases, chiefly in the continental clinics. I refer to the use of heavy dosage of estrogen or testosterone. I have the impression that such hormonal therapy has actually produced a reduction in the gonadotrophic titer, but has not been effective in cure.

It may again be emphasized that choriocarcinoma metastasizes chiefly by the blood stream, as does a sarcoma, and not regionally to the lymph glands, as does a carcinoma. Knowledge of this simple fact would deter one from any such radical pelvic operation as was done in one of the cases which we described.

Finally, as chairman of the Chorionepithelioma Committee, I would be very derelict if I did not express our gratitude for the generous comment made by Dr. Thompson, and also thank his fine organization again, as I did at the business meeting yesterday, for the support which has already been given our work and the further support which is promised for the future.

FIBROMA OF THE OVARY WITH ASCITES AND HYDROTHORAX—MEIGS' SYNDROME*

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IN 1936 before this Society Meigs and Cass reported seven patients with fibroma of the ovary with ascites and hydrothorax cured by removal of the fibroma. The paper was published in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY in 1937.[56] In 1943 Meigs, Armstrong, and Hamilton reported 27 cases of this syndrome.[58] Since that time the number of reported cases has increased rapidly so that hardly a year goes by without new case histories to be found in the literature. This study of the syndrome was undertaken to determine the number reported, to sift out those cases not properly within the scope of the syndrome, and to review any newer pertinent theories of the occurrence of the ascites and the chest fluid. This is not a complete survey of the literature; it does cover all the cases reported in the English language and a few scattered ones in French, German, and Italian. The foreign reports have been catalogued and their translation begun, but since their review has not been completed as yet they are not included at the present time.

If the foreign reports are similar to those already examined in the English literature the only forthcoming material will be additional cases and credit for priority. This latter question has already been raised and without doubt many cases were reported previous to my first report in 1934, in *Tumors of the Female Pelvic Organs,*[55] and references to those articles will be found in this paper. The problem is to give credit to those whose cases antedated ours. As was mentioned in our 1937 report the literature was reviewed as carefully as possible for the twenty-five previous years. There had been no papers describing this type of case and its treatment other than as an incidental finding among other tumors of the ovary being presented. John Cass and I were able to find 7 cases in all: 4 from our own hospital, 2 reported by Hoon from the Mayo Clinic,[34] and 1 by Leo in the *Il medico pratico.*[49] As time went on more and more were added in subsequent publications by us and by others. Since then there have been reported and placed in this syndrome a group of confusing cases. The time has come to review them all and to redefine the syndrome; and perhaps later to report the discarded ones with ascites and hydrothorax, but not Meigs' syndrome, in another report.

For this particular paper we have attempted to obtain all references to ovarian tumors with ascites and hydrothorax that could be found in the *Index Medicus* 1900-1916, in the *Quarterly Cumulative Index* 1916-1950, and the *Cur-*

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rent List of Medical Literature (Armed Forces Medical Library) 1950-1952, and, in addition, any other cases mentioned in the above references or brought to our attention through personal communications. The list of references is formidable and the task of complete review a lengthy one, so I trust that this discussion, though not complete, will be accepted as a very fair sample and estimate of the entire literature. At a future date, when the foreign reports have been translated, a further report will be made of the cases and anything else of importance that is found, thus bringing the subject completely up to date.

Historical

So far as can be determined from our study, Spiegelberg[81] in 1866 first reported upon a patient who died without operation, who complained of a swelling of the abdomen, and who had a fluid wave and at autopsy showed a left pleural effusion. She had pain and anorexia and was definitely emaciated. Her fibroma weighed 60 pounds and measured 51 by 46 by 23 cm. In 1882 Spencer Wells[92] in a treatise on ovarian tumors and uterine tumors stated on page 48 that he had seen and treated a patient in 1872 who had a large quantity of fluid in both peritoneal cavities. He mentioned other patients in the same discussion. There is no suggestion of hydrothorax. On page 83 in discussing ovarian tumors in general, he stated that with such growths "the vital organs in the chest suffer in many ways and the chest symptoms of oppressed action are often among the most tormenting. Edema, ascites, and pleural effusion, especially on the right side, occasion the greatest aggravation of misery." He further stated that sometimes after ovariotomy the chest will not return to normal and the patient dies. I infer that some of the patients recovered. Wells did not state that such tumors were fibromas but calls them tumors.

Gaillard Thomas[88] in 1877 mentioned the occurrence of fluid in the chest with ovarian lesions. Fibroma was not specified. Cullingworth[9] in 1879 in the *Transactions of the Obstetrical Society of London* reported the first real case of this syndrome in a patient who died. However, as one of the essential features of the syndrome—the fact that removal of the fibroma cures the hydrothorax—could not be determined in this particular case, it is not entirely satisfactory. Demons[11] of Bourdeaux, France, in 1887, in an excellent discussion before the Société de Chirurgie of Paris reported that 9 of 50 patients with ovarian cysts were cured of their ascites and hydrothorax by removal of the cyst.

Here again something is lacking from the true definition of the syndrome, for he speaks of cysts and not of fibromas, and in the true syndrome it is necessary that the lesion be a benign solid tumor. Pascale[64] in Italy in 1888 found the ascites and hydrothorax syndrome in 3 of 21 cysts of the ovary. He stated, according to Resinelli,[67] that with puncture of the cyst the fluid disappeared for a time but it reaccumulated and later removal of the cyst caused it to go permanently. Cysts and cystomas are not considered as properly included in the Meigs' syndrome because of the possibility that such a cyst will become

malignant or is potentially malignant at the time of the operation. To include ovarian cysts in the syndrome is to make it difficult to exclude malignant ovarian tumors, and they are not in the true syndrome.

In 1892 in the *Medico-Chirurgical Transactions* Lawson Tait[85] of England reported a true single case of this syndrome; it was a fibroma. Both ascites and hydrothorax were present, and removal of the tumor cured the patient. He wrote that after seeing about 20 cases with pleural effusion complicating abdominal disease he thought all patients deserve abdominal exploration, even though the fluid is bloody at tapping. Thus Tait reported and advised wisely on this particular syndrome. Resinelli[67] of Italy, in 1897, gave a most satisfactory review of pleural fluid and ovarian tumors. His historical review was excellent and from his article we have obtained many references to cases which would otherwise have been lost. His own report, though a thorough treatise on ovarian tumors and pleural fluid, did not include any case with the true syndrome as we understand it today. Demons,[12-14] reporting again of his experiences in 1900, 1902, 1903, wrote on fibroma of the ovary and ascites and hydrothorax and mentioned 3 patients with fibroma of the ovary with ascites and hydrothorax who were cured by removal of the fibroma. His 1903 paper gave an excellent case history and report of the essentials of the syndrome and stated, "Many times I have called attention to the fact that certain benign abdominal tumors can be accompanied by ascites, edema of legs, and pleural effusion, unilateral or bilateral, or by a change in health resembling more or less a cachectic condition—all the phenomena especially connected with, as one knows, malignant tumors at certain times in their progress. Edema of the legs is common." He advised not waiting to attack the ascites and pleural effusion by tapping but to proceed, if possible, at once to the removal of the causative lesion, the ovarian tumor. His patient was discharged as cured; effusion, ascites, and edema of legs cleared directly. In the discussion of his presentation in 1887 Terrier, Bouilly, Terillon, and Verneuil had also seen fluid in the abdomen and chest in the presence of ovarian cysts or cancers.

Dr. Funck-Brentano[20] of Paris, France, has shown great interest in this syndrome and feels that it should be divided into various categories such as (1) the true syndrome, (2) patients with hydrothorax and no fluid in the abdomen (I have never seen one), and (3) ovarian fibromas with ascites alone. With this I do not agree. However, his most important contribution to this subject is the opinion that Demons should by priority have his name precede that of Meigs in the name of the syndrome. I am sure that his name would greatly honor mine and I would be very happy to have the change. This syndrome was not named by me but by Rhoads and Terrell[69] when they reported their case in *The Journal of the American Medical Association* in 1937. They stated that Meigs and Cass's paper "first reports this syndrome completely and emphasizes its significance." Undoubtedly the syndrome had been recognized before but for thirty-four years, since Demons' discussion in 1900, no reports were made in the literature and no teaching in papers, texts, or medical schools could be ascertained. If Dr. Cass and I deserve any credit it is that we awakened the

profession to the importance of chest fluid and ascites in benign ovarian fibromas.

The references, giving the source of information for the cases to be discussed, will be listed in this paper; no one has any great numbers. Although I had not seen one for over eight years we are including in this paper a patient treated in 1952 at the Massachusetts General Hospital. The syndrome is constantly in the minds of our hospital staff.

It is interesting that Cullingworth,[9] and especially Tait[85] and Demons,[11-14] knew and wrote about this syndrome and yet it was neglected by others for many years after their very important observations.

Definition

A study of all cases of abdominal tumors with ascites and hydrothorax has made it clear to me that Meigs' syndrome must have a precise definition. It would be best to limit the syndrome to the special types of tumors that were described in the paper written and published in 1937. First, the tumor must be a benign and solid tumor with the gross appearance of a fibroma. A thecoma is a fibrous tumor and without special stains cannot be differentiated from a fibroma. We know now that thecomas and granulosal-cell tumors are most often mixed tumors and therefore these tumors, thecomas and granulosal-cell tumors, are included in the syndrome. As thecal-cell and granulosal-cell tumors were not universally recognized until about 1936, it is very possible that some of the lesions designated as fibromas might easily be called thecomas or granulosal-cell tumors now. It thus seems correct to include these tumors which in the main are fibrous, hard, solid, and benign in the group of tumors responsible for the syndrome, so as the *first* characteristic we must have a fibroma or a fibroma-like tumor; *second,* this tumor must be accompanied by ascites. Funck-Brentano[20] believes that there are cases of the syndrome without abdominal fluid, but in all cases reviewed for this paper fluid was present in the abdomen, though it was not always possible to detect it before operation. The fluid may be of very great or of small amount, but it must be there. *Third,* there must be fluid in the chest. This fluid is most often found in the right thoracic cavity but can occur in the left, and even in both sides. In some patients the fluid was diagnosed only by x-ray pictures or fluoroscopy and, although in this series such cases have been included, it might be better to exclude them and retain only those in which chest taps have been done and the fluid positively demonstrated. *Fourth,* the removal of the benign ovarian solid tumor must relieve the patient of her ascites and chest fluid. In an occasional report the fluid was relieved, only to have it appear again later when it became obvious that the tumor had been misdiagnosed and really was a malignant one. Such cases are not included in this report. It is not necessary that the fluid always be clear and yellow; it can be bloody or serosanguineous, but this is not common. This must be emphasized, for many believe bloody fluid indicates a malignant lesion. Therefore, the syndrome consists of a fibroma-like, benign tumor, and fluid in both the abdomen and the chest. The fluids must disappear and not recur following removal of the ovarian tumor.

Description of Other Lesions With Similar Findings

In the course of the review of the literature other groups of cases or single cases were discovered with similar findings, but it must be realized that almost any sort of abdominal or pelvic lesion may produce ascites and hydrothorax. It is important to preserve for the Meigs' syndrome the type that is by far the most common cause even though on a percentage basis of ovarian tumors fibromas are actually much less common. In this series of 122 cases 84 were typical cases of Meigs' syndrome, 69 were reported as fibromas, 8 as thecal-cell tumors, and 5 as granulosal-cell tumors; one was a Brenner tumor, and in one the pathologist avoided classifying the fibrous tumor. The percentage of typical cases of Meigs' syndrome was out of all proportion to other lesions that produce the same symptoms. There were 15 cases of benign ovarian cysts, a very small number considering the frequency of such cysts compared to the fibromas of the ovary. Five patients with fluid in the abdomen and chest had leiomyomas of the uterus. There were 2 teratomas of the struma (thyroid) type. There was one papilloma of the Fallopian tube, and one patient had a pelvic mass so mixed up with an inflammatory process that the pathologist did not know exactly what to call it; tuberculosis was suspected but could not be proved. In this benign group, therefore, fibromas were about four times as common a factor as the other pathologic findings, some of which actually occur about five times as frequently as fibromas.

In the malignant group, and it is certain that some of these tumors have pleural effusions that are not due to malignant extensions to the chest, there were a total of 14 such cases—9 of the malignant papillary cystadenoma type; one, a Krukenberg tumor; one, an adenocarcinoma of the round ligament with an accompanying papillary cystadenoma; one was a carcinoma of the ovary; one was a malignant papillary cystadenoma with an adenocarcinoma of the body of the uterus; and another was called a fibrosarcoma of the ovary. Thus in this much more frequent pathologic group but 14 cases were found that could be placed in a similar category to the true Meigs' syndrome. In addition to these 122 cases there were 8 patients with various lesions of the pancreas. These were a benign congenital cyst and posttraumatic injuries to the pancreas. One had a cancer of the pancreas with the same findings as in the syndrome. Therefore, it is clear that a division should be made. Inasmuch as the fibroma group is by far the most common cause, it appears that there must be some definite reason for it in this type of tumor. These tumors should be placed in a different category from the rest and should have the designation of Meigs' syndrome.

To recapitulate, there are four groups of patients that may have fluid in the abdomen and fluid in the chest. The removal of the tumor will relieve the chest fluid in some cases permanently and in some, temporarily. These are (1) the true Meigs' syndrome; (2) benign cysts of the ovary, leiomyomas, teratomas, etc.; (3) malignant lesions of the ovary; and (4) cysts and traumatic injuries to and cancer of the pancreas. Various other diseases such as heart, kidney, and liver diseases, and certain subdiaphragmatic inflammatory

lesions will cause fluid in the abdomen and chest but these cannot be cured by removal of the ovary, nor can the pancreatic lesions. The reason for not including cysts, teratomas, and fibroids is that the cysts may be potentially malignant, the leiomyomas are so common and yet so rare as causative agents in the production of the syndrome, and teratomas are definitely of a suspicious make-up. It seems best to include only the fibroma series in the true Meigs' syndrome. In another paper discussion and analysis will be made of the groups of cases not included in the syndrome but whose symptoms and physical findings have been cured by removal of an ovarian lesion.

Material for This Report

A chart (Table I) is included in this article of the 84 cases, giving the age, marital status, complaints of the patient, location of the tumor, whatever information can be had of the chest and abdominal fluids, date of operation, and date of publication of the reported cases. The literature has been reviewed and the references are given so that anyone interested may look up each case for complete details. It would be impractical to give a case history of each patient in such a report as this. In discussing this material, interesting findings will be noted.

It was stated by Demons[11] (1887), in discussing cysts of the ovary with fluid in the abdomen and chest, that the side of the chest involved was nearly always on the side of the tumor growth. This appears so in some instances and it may be that such a finding has a bearing on the reason for the presence of fluid in the chest. It is extremely difficult to see why this should be so. In this study a left-sided tumor was accompanied by fluid in the right side of the chest in 22 patients and there was left-sided fluid with a left-sided tumor in three cases. A right-sided tumor gave rise to fluid in the left side of the chest in two cases and a right-sided tumor to fluid on the right in 20 cases. Bilateral chest fluid was present with left, right, and bilateral tumors. It is evident that this finding plays no part in the reasons for fluid in one side or the other. The incidence of ascites accompanying fibromas is given as between 1 and 40 per cent.

In our own series of fibromas at the Vincent Memorial Hospital and the Massachusetts General Hospital, the incidence of abdominal fluid is about 13 per cent—a figure that falls between that of Kermauner,[41] who in a huge number of ovarian tumors found but one with fluid in the abdomen, and those of Rubin[73] of 21 per cent, and Peterson[66] of 40 per cent. That fibromas are not infrequently accompanied by ascites is obvious. The amount of fluid in the abdomen does not always reflect the amount to be found in the chest, for in some cases the abdominal fluid is not suspected and is not found until the abdomen is opened. The reverse is also true. There may be an enormous amount of abdominal fluid with a minimum of chest effusion. The embarrassed respiration is not always due to the fluid in the chest, for dyspnea may be caused by the amount of abdominal fluid plus the size of the ovarian lesion. From our study it is clear that the amount of fluid in the abdomen or the chest does not depend upon the size of the abdominal tumor. It is important

TABLE I. SUMMARY OF EIGHTY-FOUR CASES OF FIBROMA OF THE OVARY WITH ASCITES AND HYDROTHORAX

CASE NO.	AUTHOR	DATE OF OPERATION	DATE OF PUBLICATION	AGE OF PATIENT	MARITAL STATUS	NO. OF CHILDREN	COMPLAINTS	LOCATION OF TUMOR	LOCATION OF EFFUSION IN THORAX	NO. OF THORACENTESES	NO. OF ABDOMINAL TAPS	TYPE OF FLUID	
												ABDOMEN	CHEST
1	Spiegelberg, O.[81]	No operation	1866	37	M	2	Abdominal swelling, cough, dyspnea, loss of strength, anorexia, pain	??	Left	0 (autopsy)	2	Bloody serous	??
2	Cullingworth, C. J.[9]	9-10-1879	1879	36	M	5	Abdominal swelling, loss of weight, dyspnea, menorrhagia	Bilateral	Left	0 (autopsy)	0	??	??
3	Terrier, M. F.[87]	2-14-1888	1888	77	M	1	Abdominal swelling, leg swelling, cough, anorexia	Bilateral	Bilateral	0	0	Yellowish reddish	??
4	Tait, Lawson[85]	3-5-1891	1892	36	S	0	Abdominal swelling leg swelling, cough, dyspnea	Right	Bilateral	3	30 plus	Clear yellow	Bloody, yellowish
5	Demons, Albert[12]	???	1900	?? (young lady)	?	?	Leg swelling (?? other symptoms)	???	Bilateral	???	??	??	??
6	Demons, Albert[12]	????	1900	?? (older woman)	?	?	Leg swelling (?? other symptoms)	???	Bilateral	??	??	??	??
7	Meigs, J. V., and Cass, J. W.[56]	9-20-01	1937	42	S	0	Right chest pain, leg swelling, cough, dyspnea	???	Right	5	2	Straw colored	Clear
8	Meigs, J. V., and Cass, J. W.[56]	6-10-02	1937	55	M	1	Abdominal tumor, chest pain, pleurisy	Right	Right	5	0	Yellow, clear	??
9	Demons, Albert[14]	6-18-02	1903	48	M	1	Abdominal swelling, leg swelling, cough, dyspnea	Right	Right	0	1	Nonsanguineous	??
10	Meigs, J. V., and Cass, J. W.[56]	12-12-08	1937	38	M	2	Abdominal swelling, pain in back, shoulder, and left side, leg swelling, dyspnea	Left	Left	5	5	Clear yellow	Pale yellow
11	Hoon, Merle R.[34]	8-16-17	1923	36	M	1	Abdominal swelling, loss of weight	Right	Bilateral	1	0	??	??

12	Hoon, Merle R.[34]	12-9-20	1923	53	M	0	Abdominal pain, scapular pain, dyspnea, abdominal swelling	Right	Right	3	1	Clear straw colored	Clear, straw colored
13	Leo, C.[49]	7-25-26	1926	64	?	?	Chest pain, cough, dyspnea	Left	Right	Repeated	0	Greenish yellow	??
14	de Rouville, G., et al.[72]	5-10-28	1928	58	M	2	Abdominal swelling, leg swelling, cough, dyspnea, emaciation	Right	Left	1	10	Yellow	Yellow
15	Calmenson, M., et al.[7]	Sept., 1929	1947	59	M	?	Abdominal swelling	??	Left	0	0	??	??
16	Bomze, Edward J., and Kirshbaum, Jack D.[3]	9-16-30	1940	37	M	7	Abdominal swelling, abdominal pain, leg swelling	Left	Bilateral	2 (autopsy)	0	Reddish brown (autopsy)	Brownish
17	Healy, William P.[30]	12-1-31	1943	48	S	0	Abdominal swelling, abdominal pain, leg swelling, loss of weight, dyspnea	Bilateral	Left	1	1	Amber	Amber
18	Salmon, U. J.[74]	April, 1932	1934	52	M	?	Abdominal swelling, abdominal pain	Right	Bilateral	3	0	Amber	Amber
19	Calmenson, M., et al.[7]	March, 1933	1947	49	S	0	Dyspnea	Right	Right	4	0	??	?? (Identical)
20	Meigs, J. V., and Cass, J. W.[56]	8-18-34	1937	52	S	0	Abdominal swelling, changes in bowel habits, dyspnea	Left	Right	Repeated	1	Yellow	??
21	Miller, Richard H.[60]	7-16-36	----	60	S	0	Abdominal pain and pressure, weakness	Right	???	3	0	??	??
22	Weld, Stanley B.[91]	August, 1936	1938	55	?	?	Abdominal swelling, back pain	Bilateral	Right	0	0	Straw colored	??
23	Weld, Stanley B.[91]	9-18-36	1938	50	M	?	Abdominal swelling, abdominal pain, difficulty in voiding	Right	Right	0	0	Blood tinged	??
24	Macomber, Donald[53]	2-15-37	----	32	S	0	Abdominal swelling, dyspnea	Left	Right	2	1	Clear	Straw colored
25	Rhoads, J. E., and Terrell, A.[69]	3-4-37	1937	57	M	3	Loss of weight, cough, dyspnea, fatigue	Right	Right	5	0	??	??

TABLE I—CONT'D

CASE NO.	AUTHOR	DATE OF OPERATION	DATE OF PUBLICATION	AGE OF PATIENT	MARITAL STATUS	NO. OF CHILDREN	COMPLAINTS	LOCATION OF TUMOR	LOCATION OF EFFUSION IN THORAX	NO. OF THORACENTESES	NO. OF ABDOMINAL TAPS	TYPE OF FLUID	
												ABDOMEN	CHEST
26	Bomze, E. J., and Kirshbaum, J. D.[3]	11-22-37	1940	45	M	?	Abdominal mass, pain in chest, leg swelling, weight loss, dyspnea	Left	Left	0	0	Serous	??
27	Vogt, Clifford[90]	1938	1940	44	M	?	Abdominal swelling, abdominal pain, leg swelling, cough, dyspnea, anorexia	Left	Left	1	1	Bloody	Bloody
28	Harris, F. I., and Meyer, M. A.[29]	8-1-39	1941	67	M	2	Chest pain, loss of weight, dyspnea, fatigue	Left	Right	2	0	Clear, straw colored	Yellow
29	Borg, Charles[5]	8-4-39	1941	44	M	7	Abdominal swelling, abdominal pain, dsypnea	Bilateral	Bilateral	2	1	Straw colored	Pale greenish. Straw colored
30	Hendersen, A. T.[31]	11-9-39	----	42	?	?	Dyspnea	Bilateral	Right	4	0	??	??
31	Lock, Frank R., and Collins, Conrad[50]	3-21-40	1941	31	M	1	Abdominal swelling, abdominal pain, cough, dyspnea	Left	Right	0	0	Clear	??
32	Traut, H. F., and Marchetti, A. A.[89]	???	1940	??	?	?	???	??	??	??	??	??	??
33	Breen, J. V., and Nelligan, T. H.[6]	11-15-40	----	23	S	0	Abdominal swelling, frequency of urination, dyspnea	Right	Right	1	0	Straw colored	Clear, yellow
34	Ritvo, Max[71]	12-31-40	1942	57	M	?	Leg swelling, loss of weight, dyspnea, pressure	Left	Right	2	0	Yellow, clear	Blood tinged
35	Lawlor, Mary K.[43]	1940	1944	35	S	0	Abdominal swelling, dyspnea	Left	Right	1	0	??	??
36	Glass, Morris, and Goldsmith, J. W.[27]	3-28-41	1942	73	?	?	Abdominal swelling, leg swelling, dyspnea	Right	Right	1	0	Straw colored	??

37	Meigs, J. V., et al.[58]	4-5-41	1943	66	M	0	Pain in scapula, leg swelling, cough, dyspnea	Left	Right	4	0	Stained with India ink (Identical)	Greenish yellow
38	Meigs, J. V., et al.[58]	6-13-41	1943	51	M	2	Cough, dyspnea	Left	Right	3	0	Stained with dye (Identical)	Straw colored
39	Jones, W. N.[38]	10-28-41	1943	50	M	2	Abdominal tumor, leg swelling, loss of weight, dyspnea, weakness	Left	Bilateral	0	0	Clear amber	??
40	Perlmutter, Martin[65]	11-24-41	1944	60	M	1	Abdominal swelling, chest pain, loss of weight, cough, dyspnea	Right	Bilateral	10	0	Straw colored	Straw colored
41	Herrick, W. W., et al.[32]	2-16-42	1943	75	M	5	Leg swelling, dyspnea, weakness	Bilateral	Right	Repeated	0	Clear yellow	Straw colored
42	Taylor, Howard C., Jr.[86]	May, 1942	1943	72	M	6	Abdominal tumor, abdominal discomfort, fluid in chest	Right	Right	1	0	??	??
43	Keleman, Edward[40]	9-30-42	1944	49	M	?	Diaphoresis, cough, dyspnea, weakness	??	Right	Repeated	Repeated	Clear serous	??
44	Wooldridge, Wilfred[94]	June, 1943	1948	52	S	0	Chest pain, dyspnea, fatigue	Left	Right	3	0	Clear	Yellow, serosanguineous
45	Mendel, Evri, and Tyrone, Curtis[59]	7-7-43	1944	44	S	0	Abdominal swelling, abdominal pain, cough, dyspnea, amenorrhea	Left	Right	0	0	Amber	??
46	Erez, Nasid[17]	7-19-43	1945	26	M	1	Abdominal swelling, dyspnea	??	Right	3	0	Blood stained	Serofibrinous, dark yellow
47	Katz, David[39, 45]	3-3-43	----	69	M	0	Abdominal swelling, leg swelling, dyspnea	Left	Bilateral	5	1	??	Clear, straw colored
48	Fusaro, William J.[22]	8-30-43	1947	24	S	0	Abdominal swelling, abdominal pain, amenorrhea	Bilateral	Right	2	0	??	Pale, straw colored
49	Gardiner, R. H., and Lloyd-Hart, V.[24]	9-30-43	1944	38	M	0	Pain in back and knee, swelling of legs, dyspnea	Left	Right	2	0	Clear, straw colored	Clear, straw colored

TABLE I—CONT'D

CASE NO.	AUTHOR	DATE OF OPERATION	DATE OF PUBLICATION	AGE OF PATIENT	MARITAL STATUS	NO. OF CHILDREN	COMPLAINTS	LOCATION OF TUMOR	LOCATION OF EFFUSION IN THORAX	NO. OF THORACENTESES	NO. OF ABDOMINAL TAPS	TYPE OF FLUID	
												ABDOMEN	CHEST
50	Dockerty, M. B., and Masson, James C.[16]	11-15-43	1944	43	M	1	Abdominal mass, dyspnea	Left	Bilateral	4	0	??	??
51	De Normandie, R. L.[15]	11-25-43	----	47	?	?	Abdominal swelling, leg swelling, cough, passage of large vaginal clots, anorexia	Left	Right	1	1	Clear yellow	Clear yellow
52	Gild, Albert[26]	1943	1943	30	M	0	Abdominal pain, loss of weight, cough, dyspnea, diarrhea	Right	Right	1	0	Clear yellow	Opalescent
53	Massachusetts General Hospital	5-12-44	----	56	M	1	Abdominal mass, leg swelling, loss of weight, dyspnea, night sweats	Right	Left	1	1	Clear	??
54	Clay, A., et al.[8]	1944	1944	59	S	1	Abdominal mass, dyspnea	Left	Right	1	0	??	Straw colored
55	Clay, A., et al.[8]	1944	1944	47	M	1	Abdominal swelling, dyspnea	Right	Right	Repeated	1	??	Clear
56	Jaffin, Abraham E.[37]	8-1-44	1951	54	M	1	Abdominal swelling, loss of weight, weakness	Right	Right	4	1	Clear, serous	Crystal clear
57	Simon, Herbert J.[78]	9-18-44	1947	55	S	0	Weakness, mass in groin, cough, anorexia	Right	Bilateral	1	0	Clear, straw colored	Clear yellow
58	Calmenson, M., et al.[7]	Sept., 1944	1947	67	S	0	Abdominal swelling	Right	Right	0	0	??	??
59	Rubin, I. C., et al.[73]	??	1944	58	M	3	Abdominal swelling, leg swelling, dyspnea	Left	Right	3	1	??	??
60	Slaney, G.[79]	4-5-45	1946	60	M	0	Pressure in chest, loss of weight, palpitation, dyspnea, anorexia	Right	Right	1	0	Straw colored	Straw colored

61	Long, Albert E.[51]	June, 1945	1948	53	M	4	Vaginal spotting, excessive growth of body and facial hair, cough, dyspnea, abdominal swelling	Left	Right	Repeated	0	??	Sanguineous
62	Stein, Irving, and Elson, Ralph[84]	July, 1945	1948	68	M	2	Abdominal swelling, abdominal pain, cough, dyspnea	Bilateral	Right	2	0	Straw colored	Dark amber
63	Schaffner, V. D., and Kirkpatrick, T. A.[75]	11-10-45	1946	61	M	6	Vague epigastric distress, cough, dyspnea, weakness, leg swelling	Right	Right	Repeated	0	??	Slightly turbid
64	Stearns, Howard C.[83]	1-26-46	1951	54	M	1	Leg swelling, cough, dyspnea, loss of energy	Right	Bilateral	6	0	Clear	Slightly cloudy, yellow
65	Frankenthal, L. E., Jr.[84, 18]	3-16-46	1947	44	M	0	Abdominal mass, dyspnea	Left	Right	5	0	Clear	Clear, straw colored
66	Calmenson, M., et al.[7]	4-23-46	1947	71	M	?	Abdominal swelling, loss of weight, dyspnea, weakness	Bilateral	Right	11	1	Clear	Pale amber
67	Huang, C. C., and Chen, J. H.[36]	6-26-46	1948	52	M	1	Abdominal tumor, dyspnea	Left	Right	0	0	Straw colored	??
68	Spurney, Paul M.[82]	5-12-47	1948	42	S	0	Abdominal lump, dyspnea	Right	Bilateral	2	1	Blood tinged	Blood tinged
69	Marshall, A. G.[54]	7-11-47	1949	37	M	1	Abdominal swelling, dyspnea	Right	Bilateral	4	1	Straw colored	??
70	Whitehouse, W. R., and Kimbro, R. W.[93]	7-30-47	1948	48	M	3	Abdominal swelling, dyspnea	Left	Right	3	0	Straw colored	??
71	Slovin, Isadore, and Nealon, James[80]	11-23-47	1951	20	S	0	Abdominal swelling, back and chest pain, cough, dyspnea, weakness	Left	Right	1	1	Clear yellow	Dark, straw colored
72	Ridley, John H.[70]	12-22-47	1949	35	M	2	Chest and abdominal pain, loss of weight, fatigue, night sweats, dyspnea, cough, anorexia	Right	Right	4	0	Blood tinged	Blood tinged
73	Bonar, L. D., and Beatty, O. A.[4]	12-30-47	1950	44	?	?	Abdominal mass	Right	Right	2	0	Clear	Clear

TABLE I—CONT'D

CASE NO.	AUTHOR	DATE OF OPERATION	DATE OF PUBLICATION	AGE OF PATIENT	MARITAL STATUS	NO. OF CHILDREN	COMPLAINTS	LOCATION OF TUMOR	LOCATION OF EFFUSION IN THORAX	NO. OF THORACENTESES	NO. OF ABDOMINAL TAPS	TYPE OF FLUID	
												ABDOMEN	CHEST
74	Lawson, James G.[44]	2-7-48	1950	48	M	2	Abdominal swelling, vaginal bleeding, dyspnea	Left	Right	6	0	Similar to chest fluid	Clear, straw colored
75	Funck-Brentano, P.[19]	??	1948	66	?	?	??	Right	??	1	?	??	??
76	Arthur, H. R.[2]	Jan., 1949	1950	59	M	?	Abdominal swelling, cough, dyspnea	Right	Right	2	1	Clear at first, subsequently blood stained	??
77	Daland, Ernest M.[10]	8-5-49	----	40	S	0	Abdominal swelling	Right	Bilateral	0	1	Clear yellow	??
78	Lawson, James G.[44]	8-23-49	1950	44	M	1	Abdominal swelling, leg swelling, abdominal discomfort, dyspnea	Right	Right	7	2	Straw colored	Straw colored
79	Lawson, James G.[44]	12-31-49	1950	63	M	13	Abdominal swelling and discomfort, constipation, occasional nausea, dyspnea	Left	Right	1	1	Clear	Dark
80	Gambee, Louis P.[23]	3-2-50	----	48	M	0	????	Right	Right	2	2	Clear, straw colored	??
81	Hilliard, George W., et al.[33]	1-26-51	1953	57	?	?	Abdominal swelling and pain, dyspnea	Right	Bilateral	1	0	Straw colored	Straw colored
82	Nwokolo, Chukuedu[63]	5-4-51	1952	56	M	?	Abdominal pain, cough, dyspnea	??	Right	1	0	Slightly bloody	Straw colored
83	Louros, N.[52]	1952	----	42	M	Yes	Abdominal swelling, slight abdominal pain, dyspnea	Left	Bilateral	0	0	Yellowish	??
84	Massachusetts General Hospital	10-19-52	----	50	M	0	Abdominal swelling	Right	Bilateral	0	2	Dark yellow	??

to note that the next day after a chest is tapped one may find a similar amount already reaccumulated in the same chest cavity. This would suggest that there must be very wide channels to allow the ascites to run into the chest. Herrick, in discussing our paper[58] in 1943 and in his own paper[32] in 1943, states that this type of pleural effusion is never accompanied by fever. This is true, for except in those cases where the hydrothorax became infected following the opening of the chest and placing of a tube in it, or following simple chest tap, none of the 84 patients had a fever. In one patient treated by Hsu[35]—not included in this series—a pseudomucinous cyst was found floating in the pseudomucinous abdominal fluid, and at chest tap the same type of fluid was removed from the chest. This finding is important for the material is so different from the usual type. The fluid must go through the diaphragm and the channels must be of fair size or the lymphatics distended.

The diagnosis of Meigs' syndrome was considered before operation in 31 patients. Familiarity with the syndrome is a very good sign for as a rule it is the gynecologists who know about the lesion and not frequently enough the internist and surgeon. In this series bloody fluid was found in the chest and abdomen in 3 cases, in the abdomen alone in 5 cases, and in the chest alone in 4 cases. In some cases the fluid was blood stained at the time of operation perhaps from contamination with the blood in the abdominal wound; and in the chest, from injury to a pleural cavity blood vessel; but in a few cases the bloody fluid was real. Bloody fluid therefore does not always indicate the presence of a malignant tumor; it can be found in patients with a benign fibroma. Marshall[54] in his report states that he found at autopsy in a patient with blood in the peritoneal cavity due to trauma that there was blood in both chest cavities in small quantities (this case is not included in this series). Vogt[90] reported a case of fibroma (granulosal) with fluid of a serosanguineous type in the abdomen and chest (Case 27). Bloody fluid in the abdomen and chest was also found in the cases of Spurney[82] (Case 68) and Ridley[70] (Case 72). In all instances operation relieved the condition and there was no reaccumulation of such fluid. Long,[51] in a paper upon the subject of hemothorax in relation to benign pelvic tumors, reports a case of a patient with a mesenchymoma (in the fibroma series) with bloody fluid in the chest (Case 61). Following radiation therapy of the ovarian tumor the chest fluid disappeared. In this case no mention is made of fluid being found at laparotomy, though a fluid wave had been noted before the use of radium and x-ray treatment.

The fluid disappears from the chest very quickly; it is impossible to state accurately how early, for it depends upon how frequently the chest was percussed after operation, or the chest x-rayed, etc. It appears from the cases reviewed that the chest fluid usually disappeared in from three days to two weeks. In 6 cases it appeared to be necessary to tap the patient after operation. One (Case 82) was tapped because she was anxious to leave the hospital and the fluid had not entirely cleared. In another (Case 62) two taps were done for the comfort of the patient, shortly after the operation and five days later. Four (Cases 13, 18, 38, and 53) were tapped from 8 to 21 days after

operation. This is not a common occurrence. It is certain that with a little patience the fluid would have disappeared. Occasionally the tapping is done to relieve the embarrassment of the chest fluid in the immediate postoperative period. In others it is conceivable that the fluid might have been pocketed by adhesions within the chest.

There is interest in the problem of leg swelling. Demons[11] reported it in 1887. Nora,[62] reporting a case of pseudomucinous cystadenoma not included in this series, states that after they placed a tube in the patient's chest to relieve her dyspnea the swelling and edema of the legs disappeared. In this series of 84 cases 25 showed swelling of the legs from the ankle up, and some as high as the knee. Operation and relief from the abdominal and chest fluid also relieved the leg and foot edema.

It is obvious from a study of these cases that abdominal paracentesis was not practiced nearly as frequently as the chest was tapped. The thoracentesis was done to lighten the respiratory burden by relieving the fluid in the chest. Chest fluid reaccumulates so fast that an abdominal tap combined with the chest tap would be of considerably more value. Operation for removal of the tumor, as soon as possible, when the patient's condition permits, is the proper treatment.

In a few patients previous pelvic surgery had been performed prior to the operation for the present illness and no lesion of the ovary was found at that time; and, in others, examination before entrance to the hospital noted pelvic tumors present for at least four years before onset of symptoms. In one patient (Case 44) previous operation revealed no abnormality, yet in four years a tumor grew to 9 by 10 by 12 cm. accompanied by the typical syndrome. In another patient operated upon thirteen years after the removal of her fibroma (Case 10) many adhesions were found and a small cyst of the other ovary.

In a few cases the postoperative x-rays showed a thickened pleura and it was very difficult to tell if the fluid had completely gone from the chest cavity.

Diagnosis and Symptoms

The symptoms in the Meigs' syndrome are typical. Not all the signs are present in each case but some of them are, and a knowledge of the syndrome should at least suggest the diagnosis. Calmenson, Dockerty, and Bianco[7] say that the late W. J. Mayo made a preoperative diagnosis of fibroid tumor of the ovary in a patient in this series (Case 11) reported by Hoon[34] in 1923. Abdominal swelling and pain, dyspnea (nearly always present), chest pain, loss of weight, edema of the legs, and the signs of fluid in the chest on physical examination should at once suggest the possibility of this lesion. X-ray of the chest will show the presence of fluid or some lesion in the thoracic cavity. There are cases in this report where the patient has stated that she had had pleurisy before her admission to the hospital. If the fluid in the chest is clear and yellow and if a mass can be felt through the abdominal wall, or if after abdominal

paracentesis the fluid is found to be similar to that in the chest, and if then a tumor mass can be felt on abdominal palpation or pelvic examination the diagnosis should be made. At least it should indicate that exploration of the abdomen should be carried out. In some instances replacement of the chest fluid with air helps to rule out any metastatic mass or lung tumor. The fluid was found in the right side of the chest alone in 52 patients and it is this side that is predominantly affected. This is said to be due to the greater number of lymphatic channels found in the diaphragm on the right side. In 20 patients the fluid was in both sides of the chest; and in 9, on the left side. In 3 cases we were not able, from the patient's record, to decide on which side the fluid was located. The knowledge that clear fluid can be found in the chest in patients with ovarian cysts or malignant ovarian tumors is important and, as Lawson Tait warned many years ago, exploration should be done in spite of this finding. Chest fluid will be found in some cases of heart failure, kidney disease, or even Laennec's cirrhosis, and yet it should not be too difficult to make the diagnosis in such patients. It is said that in some cases of amebiasis fluid is found in the chest cavity; especially is this true when the liver is the seat of the infection.

Many of the patients with Meigs' syndrome are reported as undernourished, very ill, emaciated, and cachectic, and small wonder when the fluid accumulates so fast in the serous cavities. However, some patients are especially well and some very obese. It was noted in one patient in this series that at autopsy the pericardium contained fluid as well as the chest and abdomen. The liver has been reported as large, but after removal of the primary cause of the disease the liver has returned to its normal size (Cases 41 and 56). This is not always true, for in one of our patients an enlarged liver remained at its preoperative size.

Other symptoms noted in the analysis of the cases showed that there may be a shift of the heart and mediastinum to the opposite side from the fluid in the chest and that there may be a congestion and fullness of the veins in the neck. Prolapse of the uterus is not uncommon as a result of the intra-abdominal pressure, and incontinence and frequency of urination have been reported. Anderson,[1] reporting a case of malignant papillary cystadenoma (not included in this series), noted that after operation there is a marked increase of urinary excretion. Abnormal bleeding of all types has been reported, due to the illness of the patient and the interference in the young with ovarian function. After tapping of the chest an x-ray diagnosis of partial or total collapse occasionally occurs. It may not be possible to feel the tumor mass until after abdominal fluid has been removed, but usually the tumor will be found as a ballotable mass up and out of the pelvis proper. Elevation of the diaphragm has been frequently noted. Labored breathing is of course a typical symptom of the embarrassed respiration. In one patient (Case 63) Schaffner and Kirkpatrick[75] found that they were dealing with a pulmonary pleural fistula. The pleural pressure was plus six and still plus six after collapse of the lung. The lung could not be re-expanded. The chest was completely aspirated and 90

per cent collapse of the lung noted on thoracoscopic examination. The pleura was only slightly thickened but markedly red and inflamed. The lung was not atelectatic as it expanded and contracted with respiration at the time of the thoracoscopic examination. There was a bleb on the lung that probably accounted for the leak. After operation the chest condition cleared completely. It is of interest that hemoptysis is very rare. In no cases in this series did bloody sputum occur; this fact was noted by Demons. It shows that we are dealing with an effusion in the chest and not a lung or bronchial disease. There is rarely any pleural rub after the patient is truly convalescent. However, in one of our own patients (Case 10) it took over a month for the rub to disappear. It should not be difficult to make the diagnosis of this lesion. Clinical examination and x-rays are the most important, and laboratory work should substantiate the clinical findings, but will not make the diagnosis.

Laboratory Findings

The fluids in the chest and in the abdomen are very similar in a typical case of Meigs' syndrome. The fluid is nearly always clear, yellow, citron, and amber; rarely (and a few cases have been included) is there a truly bloody fluid. The specific gravity of a transudate is given as usually below 1.015 and that of an exudate as above 1.018. The fluids in this group show that many are in the 1.010 to 1.017 group. Occasionally one will be much lower and another has been reported as high as 1.040 (Case 70) but these are unusual and could be due to mistakes in reporting. It is generally conceded that most of the fluids are transudates and not exudates. An occasional case will be seen, such as Schaffner and Kirkpatrick's[75] (Case 63) where an apparent inflammatory process was seen at thoracoscopic examination. This inflammation might have been due to the ruptured bleb and the fluid actually a transudate. In many instances the patient's fluid was injected into a guinea pig to detect the presence of tuberculosis but on only one occasion was the report positive. Many smears were studied for bacteria of any sort and none found. All cultures were sterile. Smears of the type used by Papanicolaou were done on many of the recent cases and were universally negative. A sufficient number of blood nonprotein nitrogen determinations have been done to demonstrate that it is normal in this entity. The total serum protein was reported in one patient to be 3.38, 3.82, and 4.28 on three occasions but the preponderance of tests are sufficiently close to normal to satisfy us that this test means little. One was reported as 7.1 Gm. per cent. If the total protein (Case 41) should be so low as to produce this syndrome there should be more subcutaneous edema than there is. There is some, to be sure, of the ankles, legs, and chest wall (Terrier,[87] Case 3) but generalized edema is rare. Perlmutter[65] (Case 40) ten days postoperatively measured the venous pressure at 15 c.c. of saline with the arm level with the auricle, and the arm-tongue circulation measured with Decholin was 12 seconds, both of which tests are normal. The albumin in the abdominal fluid was measured by Stearns[83] (Case 64) as 40 Gm. per liter. Albumin has been found by Ridley[70] (Case 72) as 3.8 and the globulin as 1.5. The protein of the abdominal fluid measured in three different patients 2.5

Gm. per cent, 2.58 Gm. per cent, and 3.5 Gm. per cent; and the protein of the chest fluid, 2.5, 2.7, 4, 3.7, 1.7, and 5.3 Gm. per cent. In the two instances where the fluid in the chest and fluid in the abdomen were measured for protein at the same time the grams per cent were 2.5 and 2.5; and 3.5 and 3.7. Low protein in the chest fluid seems to be characteristic. There is a great predominance of lymphocytes and mononuclear cells in the smear of the chest fluid. In one instance with blood-tinged fluid the red cell count was 1,800 per cubic centimeter and the white blood cells 350. In another patient in two successive counts a count of 60 per cent lymphocytes changed to a count of 63 per cent eosinophils. There are no distinctive laboratory findings except on the negative side. It has occasionally been noted that the fluid will clot on standing, but this is not constant.

Theories and Experimental Work

There are many theories and speculations as to why the fluid is in the abdomen and in what manner it arrives in the chest.* The theory of low serum protein as a cause can probably be discarded. Selye's[76, 77] alarm reaction has definite facets that are pertinent to the etiology, yet some of the fluid had been present too long a time and in some cases the onset of the fluid appears to be too rapid for the alarm reaction to have been responsible. Leakage from the azygos vein as a cause may be discarded as fluid is also found in the left side of the chest with none on the right. The idea that fluid might be secreted in the chest from the chest lining or a lung and therefore be the cause of the effusion and ascites, is not borne out by the facts. Injections of India ink and carmine, and the experimental work of Lemon[46-48] with hydrokollag in the chest show that the pleural cavity lymphatic current is toward the retroperitoneal spaces above and near the kidney and the adrenal gland and not the abdomen. The current of flow is from the abdomen into the chest, as shown experimentally by Lemon and practically by Meigs, Armstrong, and Hamilton,[58] and also by Lawson.[44] Consideration of pleuroperitoneal tubes as a major etiological factor has been abandoned as such tubes with free communication are extremely rare and this syndrome is much more common than such congenital defects. In the paper of Meigs and associates[58] published in 1943 an important speculation was presented, "The passage of particulate carbon is of considerable interest when considered with relevance to the mechanism of hydrothorax in conjunction with ascites in certain conditions other than Meigs' syndrome. Statistical considerations enhance this interest. For Meigs' syndrome is rare in comparison with ovarian fibromas with ascites alone. So, likewise, is hydrothorax and ascites rare in comparison with Laennec's cirrhosis with ascites

*Dr. Richard Sweet has called my attention to a pleuroperitoneal sinus (the sinus of Bochdalek) as a possible channel for abdominal fluid to enter the chest. One must also consider the opening in the chest following a trauma. These two communicating spaces are open and no hernial sac is present. According to Sweet** the sinus of Bochdalek is a "small oval defect in the lateral area of the muscular portion of the diaphragm close to the costal insertion." He further states, "Although this condition may exist in either side of the diaphragm, it is usually the subject of surgical intervention only on the left because of the fact that on the right the liver prevents the passing through of any of the hollow abdominal viscera." However, it is probable that fluid would pass through. More careful exploration of the diaphragm should be carried out in Meigs' Syndrome.

**Sweet, Richard H.: Thoracic Surgery, Philadelphia, 1950, W. B. Saunders Company, pp. 21 and 317.

alone. It may be that hydrothorax is found in conjunction with ovarian fibroma or portal hypertension in those few patients who also have sufficient congenital mechanical communication between peritoneum and pleura. Extension of this hypothesis leads to investigation of the possibility of such communications in conditions where the basis of fluid in both cavities is more readily explicable, e.g., cardiac decompensation and metastatic carcinoma." The character of the fluid in the abdomen and chest is not specific for fibromas of the ovary. Inflammation in the pelvis due to the presence of the tumor as a source of the fluid can also be discarded as so few of the reported cases show changes in the peritoneum at operation. Concomitant heart or renal disease may be present in a few cases but such difficulty is unusual in the great majority of patients. Cachexia with emaciation as a cause of hypoproteinemia and thus edema is reasonable but a number of these patients are normal and well nourished and some are even obese, as stated above. Herrick[32] believes that hypoproteinemia is ruled out as there are so few patients with subcutaneous edema. Pressure on the vena cava with back pressure does not deserve very much consideration as the tumors are frequently so high and are so freely movable and ballotable. A chemical or toxic basis has been considered responsible by a few—a toxin that can reduce the permeability of the diaphragm—but no toxin or chemical has been found in the fluid. Resinelli,[68] one of the early investigators of this syndrome, believed that the chest fluid should be interpreted as a process of reaction of the pleura because of an irritational factor transferred to the diaphragm. He did not consider the fluid a pure transudate but real pleural production, determined by a toxic agent. Though it may be possible that there is such a toxin, this theory I believe is not to be considered too seriously. The question of the fluid in the chest being due to metastatic nodules from the granulosal or thecal tumors and that by removing the primary lesion the activity of the secondary growth ceases has been considered, but is certainly doubtful. Nash[61] (case not reported in this series) considered that the upward pressure on the diapragm constituted the reason for the pleural effusion. Ritvo[71] suggests that if the fluid goes through the congenital pleuroperitoneal tubes drainage of the abdomen should clear the chest effusion, but it does not, nor does air placed in the abdomen get into the chest with the patient standing, as it should if the opening is a large one. Long[51] found that radium and x-ray treatment of his mesenchymoma (? granulosal cell or arrhenoblastoma) prevented the further accumulation of fluid in the chest and in the abdomen. Tait[85] (Case 4) also noticed that after many abdominal taps the fluid did not advance or recur in his patient's chest. It is not possible to explain these two isolated phenomena but Rubin suggests that block in the minute openings in the diaphragm might prevent further chest fluid accumulation, even if the production of abdominal fluid continued. That concomitant fluid in the abdomen and chest is frequent is suggested by Marshall,[54] who states that he has never, at autopsy, found ascites without some degree of pleural effusion. Thus there must be some very simple and normal way of communication between the two cavities.

However, many authorities on chest surgery from those doing surgery on children to those doing adult surgery have been queried about openings in the chest and they state that very few open communications are ever seen during their operations; hernias are seen but openings are rare. Marshall[54] believes that hydrothorax is related not only to the size and rate of formation but is an individual characteristic of the subject. Harris and Meyer[29] (Case 28) found a distinct nest of cells with acinar arrangement in their chest fluid and wondered if such a secretory gland could account for the presence of fluid.

TABLE II (CASE 38). CARBON INJECTION

Chest fluid:	Mononuclear cells loaded with carbon
Abdominal fluid:	Mononuclear cells loaded with carbon
Blood (Buffy coat):	No carbon seen

TABLE III (CASE 37). ELECTROPHORETIC DISTRIBUTION OF PROTEINS IN CHEST AND ABDOMINAL FLUIDS

TOTAL PROTEIN	ABDOMEN 3.5 GM./%	CHEST 3.7 GM./%
Albumins	73.5%	73%
α-Globulins	5.5%	5%
β-Globulins	13.0%	13%
Fibrinogen	1.0%	2%
γ-Globulins	7.0%	7%

TABLE IV. (CASE 38). ELETROPHORETIC DISTRIBUTION OF PROTEINS IN CHEST AND ABDOMINAL FLUIDS

TOTAL PROTEIN	ABDOMEN 4.7 GM./%	CHEST 4.7 GM./%
Albumins	72.0%	72.0%
α-Globulins	4.5%	4.5%
β-Globulins	11.0%	10.5%
Fibrinogen	3.5%	4.0%
γ-Globulins	9.0%	9.0%

The studies by electrophoresis as reported by Meigs and others show fairly conclusively that the chest and abdominal fluids are the same. Tables II, III, and IV show the electrophoretic readings in their patients. Thus it is fair to search for a method to explain how fluid gets from the abdomen to the chest, as this is the way the current travels. By means of India ink injection Meigs, Armstrong, and Hamilton[58] (Cases 37 and 38) and Lawson[44] (Case 79) have shown that the passage is from abdomen to chest and not the reverse. Both findings show that the ink was in the mononuclear cells in the chest fluid. Certainly, this experiment has shown that the circulation is up from the abdomen into the chest. As suggested by Dr. John B. Graham[28] in a personal communication, it might be very valuable for thoracic surgeons to place innocent radiation-tagged material in the abdomen and try to recover it in the chests of their patients at operation. Valuable information might come from such a study. It remains, therefore, to prove how the ascites occurs. This has a great many explanations from Selye's alarm reaction, twisting of the pedicle, to adhesions as a proof of irritation. Many of the fibromas have mod-

erate adhesions that would prevent them from twisting and the twisting mechanism is further ruled out by the fact that some of the tumors are wedged in the pelvis and could not twist. One thing seems characteristic to most of the tumors and that is cyst formation within the tumor. The cysts are not lined with epithelium. This must mean injury or necrosis and this in turn suggests edema and, as Calmenson and associates[7] (Case 15), Lawson[44] (Case 79), Marshall[54] (Case 69), and Spurney[82] (Case 68) state, most tumors give evidence of edema. Calmenson and his collaborators found microscopic evidence of edema in each specimen. How to correlate this with the fluid is suggested by the work of Geibel,[25] as quoted by Rubin, Novak and Squire,[73] that after placing a fibroma in a dry pot it shrank from 3,200 Gm. to 2,050 Gm. in 24 hours. Lawson[44] also tried the experiment and found that his tumor lost one-fourth of its weight by loss of fluid from it in 24 hours. This experiment was tried by us with the same result. In our case the fibroma was placed in a jar with ligatures upon the pedicle of the tumor, thereby showing that it was the tumor that lost the fluid, not the blood vessels. Whether the pedicle was tied in Geibel's case or Lawson's case was not mentioned in their reports. Edema is more important than necrosis or cyst formation, as pointed out by Rubin, and edema is present in most of these solid tumors. It is conceivable that in this type of tumor pressure of its hard structure on the lymphatics in the tumor itself causes the escape of fluid through the surface lymphatics that are situated just beneath the single-layered cuboidal epithelium covering the tumor. As Rubin explains, the leiomyoma has a tough, fibrous capsule but not the fibroma and thus fluid is less frequently squeezed out of a leiomyoma of the uterus. The reason for the fluid in the abdomen then may be secretion from the peripheral tumor lymphatics and the forcing of fluid out of the hilar lymphatics. The edema in the tumor itself forces more fluid outside. Such explanation is speculative and is not proved, for not all fibromas are accompanied by ascites and not all with fluid in the abdomen have it in the chest. The fluid in the abdomen is the same as the fluid in the chest; particulate matter can pass the diaphragmatic barrier, thus the ascitic fluid must go the same way as the particulate matter, presumably through the subdiaphragmatic lymphatics into the supradiaphragmatic lymphatics and into the pleural cavity. Pelvic lymphatics are often very large and many times when operating for leiomyomas the surgeon is astounded by the very large lymphatics in the broad ligaments. It is possible that the fluid in the abdomen created by the presence of the fibromas may flow up such huge lymphatic chains and be delivered through the sub- and supradiaphragmatic lymphatics. Also there may conceivably be interstices between the cells of the diaphragm that will allow fluid through them with just the correct amount of pressure from below. This then is the probable etiology of the abdominal fluid and also the mode of its entering the chest.

Treatment

The proper treatment in Meigs' syndrome is removal of the primary cause, the tumor of the ovary. Inasmuch as it is always benign, except for an occa-

sional granulosal tumor, and not too frequently bilateral, simple oophorectomy should be sufficient in the young and, if both ovaries are to be removed, total hysterectomy with bilateral salpingo-oophorectomy.

Preparation of the patient for operation should be the same as for any other abdominal operation. If the chest or abdominal fluid embarrasses the patient, chest or abdominal taps should precede the operation. The removal of the tumor, by definition of the syndrome, cures the patient—and it does. To account for the rapid disappearance of the fluid from the chest and abdomen after operation it is necessary to believe that there are either very fast-moving currents from the chest into the retroperitoneal spaces and then absorption, or that the chest epithelium, blood vessels, and lymphatics can—under circumstances such as occur with relief of pressure—rapidly absorb this fluid. The same must be true of the abdominal fluid to account for the disappearance of whatever remains following laparotomy.

Results

Of our 84 patients 5 died, a mortality of 5.9 per cent, but four of them died before operation. Two patients died because operations were just not done, one died of eclampsia, one was a sudden death before operation, and one died of a metastatic cancer not related to the fibroma. The remaining patients have all done well. There have been no reported recurrences, one of the patients having been followed for as long as 27 years in perfect health. This group of patients with a lethal disease if it is not interfered with and who are extremely ill at the time of operation present a very satisfactory group of surgical patients.

Conclusions

1. From reports in the English language with a few in French, Italian, and German, 84 patients with Meigs' syndrome have been found. Many articles in foreign languages have not been translated but will be for a further report.

2. Tait[85] and Demons[12-14] reported typical cases of this syndrome in 1892, 1900, 1902, and 1903 and advised that operation upon such patients with removal of the fibroma would cure the syndrome. Others have reported the presence of fluid in the abdomen and chest in patients with ovarian tumors (not specified) and stated that removal of the tumor cured the patients' symptoms.

3. The symptoms are very typical but laboratory studies are of very little value in making the diagnosis.

4. There is a group of patients with teratomas, ovarian cysts, and malignant cysts that are not included in the syndrome. They will be reported later as a group.

5. The typical Meigs' syndrome must be (1) a fibroma-like tumor of the ovary, (2) with fluid in the abdomen, (3) with fluid in the chest, and (4) removal of the tumor must cure the patient.

6. The preoperative diagnosis was suggested in 31 out of 84 patients.

7. The cause of the fluid in the abdomen is most important for the current is from abdomen to chest and entrance into the chest is apparently not difficult to explain. The fluid in the abdomen probably comes from the edematous fibromas which can leak fluid.

8. The treatment of the syndrome is removal of the tumor and a cure can be expected.

9. Credit should be given to Dr. Funck-Brentano[21] for locating the papers of Demons and for pointing out to those interested in this syndrome that it had been described by Demons in 1887-1903. He calls the groups of cases the Demons-Meigs' syndrome with good reason.

References

1. Anderson, H. B.: Pennsylvania M. J. **47**: 671, 1944.
2. Arthur, H. R.: J. Obst. & Gynaec. Brit. Emp. **57**: 802, 1950.
3. Bomze, E. J., and Kirshbaum, J. D.: Am. J. Obst. & Gynec. **40**: 281, 1940.
4. Bonar, L. D., and Beatty, O. A.: J. Internat. Coll. Sugeons **14**: 234, 1950.
5. Borg, C.: J. Obst. & Gynaec. Brit. Emp. **48**: 750, 1941.
6. Breen, J. V., and Nelligan, T. H.: Personal communication.
7. Calmenson, M., Dockerty, M. B., and Bianco, J. J.: Surg., Gynec. & Obst. **84**: 181, 1947.
8. Clay, A., Johnston, R. N., and Samson, L.: Brit. M. J. **2**: 113, 1944.
9. Cullingworth, C. J.: Tr. Obst. Soc. London **21**: 276, 1879.
10. Daland, E. M.: Personal communication.
11. Demons, A.: Bull. et mém. Soc. de chir. de Paris **3**: 771, 1887.
12. Demons, A.: Discussion of Rocher, M. Louis: Rev. mens. de gynéc., obst. et paediat., Bordeaux **2**: 274, 1900.
13. Demons, A.: Congrès de Chirurgie, Paris, pp. 739-740, 1902.
14. Demons, A.: Rev. mens. de gynéc., obst. et paediat., Bordeaux **5**: 184, 1903.
15. De Normandie, R. L.: Personal communication.
16. Dockerty, M. B., and Masson, J. C.: Am. J. Obst. & Gynec. **47**: 741, 1944.
17. Erez, Nasid: J. Obst. & Gynaec. Brit. Emp. **52**: 506, 1945.
18. Frankenthal, L. E., Jr.: Am. J. Obst. & Gynec. **53**: 331, 1947.
19. Funck-Brentano, P.: Gynéc. et obst. **47**: 150, 1948.
20. Funck-Brentano, P.: Compte rend. Soc. franç. de gynéc. **18**: 178, 1948.
21. Funck-Brentano, P.: Presse méd., pp. 341-342, April 16, 1949.
22. Fusaro, W. J.: New York State J. Med. **47**: 1514, 1947.
23. Gambee, Louis: Personal communication.
24. Gardiner, R. H., and Lloyd-Hart, V.: Lancet **2**: 500, 1944.
25. Geibel, A.: In Henke, F., and Lubarsch, O., editors: Handbuch der speciellen pathologische Anatomie und Histologie, Berlin, 1937, Julius Springer, vol. 7, no. 3, by J. Miller. Quoted by Rubin.[73] Dissertation, Leipzig, 1902.
26. Gild, Albert: J. Obst. & Gynaec. Brit. Emp. **50**: 440, 1943.
27. Glass, Morris, and Goldsmith, Joseph W.: Am. J. Obst. & Gynec. **43**: 1048, 1942.
28. Graham, John B.: Personal communication.
29. Harris, F. I., and Meyer, M. A.: Surgery **9**: 87, 1941.
30. Healy, William P.: Discussion of Meigs, J. V., Armstrong, S. H., and Hamilton, H. H.[58]
31. Henderson, A. T.: Personal communication.
32. Herrick, W. W., Tyson, T. Lloyd, and Watson, B. P.: Arch. Int. Med. **71**: 370, 1943.
33. Hilliard, G. W., Moorehead, C., and Terhune, C. A.: J. A. M. A. **151**: 738, 1953.
34. Hoon, Merle R.: Surg., Gynec. & Obst. **36**: 247, 1923.
35. Hsu, Chien Tien: Personal communication.
36. Huang, C. C., and Chen, J. H.: West. J. Surg. **56**: Views and Reviews VIII, August, 1948.
37. Jaffin, Abraham E.: J. Mt. Sinai Hosp. **17**: 596, 1951.
38. Jones, W. N.: J. M. A. Alabama **12**: 199, 1943.
39. Katz, David: Personal communication.
40. Keleman, Edward: Am. J. Obst. & Gynec. **47**: 275, 1944.
41. Kermauner, F.: In Veit. Johann and Stoeckel, Walter: Handbuch der Gynäkologie, München, 1932, J. F. Bergmann, vol. 7. Quoted by Rubin, I. C., Novak, J., and Squire, J. J.[73]
42. Lallemand, Adolphe: Contribution a l'étude des fibromes de l'ovaire, Thèse de la Fac. Med. Paris, 1896.

43. Lawlor, Mary K.: Proc. Roy. Soc. Med. **37**: 430, 1944.
44. Lawson, James G.: J. Obst. & Gynaec. Brit. Emp. **57**: 595, 1950.
45. Lebovitz, Edward: Discussion of Stein, Irving F., and Elson, Ralph.[84]
46. Lemon, Willis S.: Am. J. M. Sc. **178**: 536, 1929.
47. Lemon, Willis S.: Am. Rev. Tuberc. **22**: 685, 1930.
48. Lemon, Willis S., and Higgins, George M.: Am. J. M. Sc. **181**: 697, 1931.
49. Leo, C.: Med. prat. **11**: 422, 1926.
50. Lock, Frank R., and Collins, Conrad G.: AM. J. OBST. & GYNEC. **41**: 517, 1941.
51. Long, Albert E.: California Med. **68**: 3, 1948.
52. Louros, N.: Personal communication.
53. Macomber, Donald: Personal communication.
54. Marshall, A. G.: J. Obst. & Gynaec. Brit. Emp. **56**: 86, 1949.
55. Meigs, J. V.: Tumors of the Female Pelvic Organs, New York, 1934, The Macmillan Company.
56. Meigs, J. V., and Cass, J. W.: AM. J. OBST. & GYNEC. **33**: 249, 1937.
57. Meigs, J. V.: Ann. Surg. **110**: 731, 1939.
58. Meigs, J. V., Armstrong, S. H., and Hamilton, H. H.: Am. J. Obst. & Gynec. **46**: 19, 1943.
59. Mendel, Evri, and Tyrone, Curtis: AM. J. OBST. & GYNEC. **48**: 271, 1944.
60. Miller, Richard H.: Personal communication.
61. Nash, G.: Lancet **1**: 378, 1919.
62. Nora, Ernest D., and Davison, Richard M.: Dis. of Chest **13**: 423, 1947.
63. Nwokolo, Chukuedu: Brit. M. J. **1**: 905, 1952.
64. Pascale: L'idrotorace nelle cisti dell'ovaio. Arch. ed atti d. Soc. ital. di chir., Naples. **5**: 291, 1888.
65. Perlmutter, M.: Ann. Int. Med. **20**: 132, 1944.
66. Peterson, R.: Am. Gynec., N. Y. **1**: 45, 1902.
67. Resinelli, G.: Ann. di ostet., Milan **19**: 721, 1897.
68. Resinelli, G.: Ann. di ostet., Milan **22**: 831, 1900.
69. Rhoads, J. E., and Terrell, Alexander W.: J. A. M. A. **109**: 1684, 1937.
70. Ridley, John H.: South. M. J. **42**: 757, 1949.
71. Ritvo, Max: Am. J. Roentgenol. **48**: 152, 1942.
72. de Rouville, G., Villa, G., Buibert, H. L., and La Fourcade, E.: Arch. Soc. d. sc. méd. et biol. de Montpellier **9**: 373, 1927-1928.
73. Rubin, I. C., Novak, J., and Squire, J. J.: AM. J. OBST. & GYNEC. **48**: 601, 1944.
74. Salmon, U. J.: J. Mt. Sinai Hosp. **1**: 169, 1934.
75. Schaffner, V. D., and Kirkpatrick, T. A.: Canad. M. A. J. **55**: 55, 1946.
76. Selye, Hans: Personal communication.
77. Selye, Hans: Nature **138**: 32, 1936.
78. Simon, Herbert J.: AM. J. OBST. & GYNEC. **53**: 1042, 1947.
79. Slaney, G.: Queen's M. Mag. **39**: 113, 1946.
80. Slovin, I., and Nealon, J.: Delaware M. J. **23**: 8, 1951.
81. Spiegelberg, O.: Monatschr. f. Geburtsh. **28**: 415, 1866.
82. Spurney, Paul M.: Ohio State M. J. **44**: 722, 1948.
83. Stearns, Howard C.: West J. Surg. **59**: 253, 1951.
84. Stein, Irving F., and Elson, Ralph: Dis. of Chest **14**: 722, 1948.
85. Tait, Lawson: Medico-Chirurgical Transactions, London **75**: 109, 1892.
86. Taylor, Howard C., Jr.: Discussion of Meigs, J. V., Armstrong, S. H., and Hamilton, H. H.[58]
87. Terrier, M. F.: Fibrome de l'ovaire droit. Prog. méd., 1888, p. 466. Quoted by Lallemand, Adolphe.[42]
88. Thomas, Gaillard: Trattatto pratico delle mallatie delle donne. Vers. ital. Firenze, 1877, p. 752. Quoted by Resinelli.[67]
89. Traut, H. F., and Marchetti, A. A.: Surg., Gynec. & Obst. **70**: 632, 1940.
90. Vogt, C. J.: AM. J. OBST. & GYNEC. **40**: 285, 1940.
91. Weld, Stanley B.: New England J. Med. **218**: 262, 1938.
92. Wells, T. Spencer: Ovarian and Uterine Tumors, Philadelphia, 1882, P. Blakiston Son and Co.
93. Whitehouse, W. R., and Kimbro, R. W.: AM. J. OBST. & GYNEC. **56**: 983, 1948.
94. Wooldridge, Wilfred: Am. J. Med. **5**: 237, 1948.

Discussion

DR. R. A. KIMBROUGH, Philadelphia, Pa.—First, I would like to call to your attention the fact that Dr. Meigs makes no claim to being the first to describe the occurrence of ascites and hydrothorax in association with fibroma of the ovary. Quite

rightly he concedes priority to Spiegelberg, Spencer Wells, Cullingworth, Demons, and Lawson Tait. Review of the literature rather firmly establishes Demons as the first to report a case with all of the essential points of this interesting syndrome.

I am in accord with Dr. Meigs' statement that the time has come to redefine the syndrome in an effort to avoid the confusion which now characterizes this clinical picture. On one page of his manuscript the author states that "the tumor must be a benign and solid tumor with the *gross* appearance of a fibroma." Following this statement he proceeds immediately to include theca-cell and graulosa-cell tumors in the syndrome. Since a certain number of the latter tumors are malignant, their inclusion seems illogical, being based as it is on gross appearance alone.

I am presuming, therefore, to offer two alternatives. First, that the syndrome include only fibromas of the ovary with associated ascites and hydrothorax as originally defined. Second, and perhaps more logical, might we not accept all ovarian tumors both solid and cystic with associated ascites and hydrothorax, *provided* there is no evidence of metastasis in the peritoneal and pleural cavities?

With Dr. Meigs' other criteria for the syndrome there can be little or no disagreement. Unfortunately, no real explanation can yet be given for the peculiar predisposition of ovarian fibromas to produce ascites nor for the associated hydrothorax in some but not all of these cases.

DR. R. R. CRON, Milwaukee, Wis.—It is well that Dr. Meigs has reviewed the literature on the Demons-Meigs' syndrome, brought up to date as completely as possible all case reports in the English literature, and especially redefined the Meigs' syndrome. Certainly in many quarters the Meigs' syndrome had been considered to be any ovarian tumor associated with ascites and pleural effusion.

The records in three of our large hospitals have been culled in an attempt to find a case that fitted into the above-mentioned syndrome, and although many ovarian fibromas with ascites were found and although about 50 per cent were subjected to pleural roentgen study, none showed effusion. There has been one patient with the true Meigs' syndrome operated upon at Milwaukee Hospital, the record of which is not available. However, I would like to record the case of a Mrs. W., aged 63, cared for by Dr. Kohn of Elkhorn, Wis., who repeatedly performed abdominal and pleural paracenteses thinking that the patient had an ovarian carcinoma until study of the pleural fluid showed no evidence of malignant or neoplastic cells. After a three-month period of observation the patient was operated upon and a 3 by 2.5 by 2 cm. left ovarian tumor was removed. It was composed of small cystic spaces containing yellow oily material which, on microscopic study, showed multinucleated foreign body type giant cells in the wall. In adjoining areas there were fibromuscular tissue and also numerous thin-walled blood vessels giving an angiomatoid appearance. A diagnosis of dermoid cyst with fibroma of the ovary was made. Upon removal of the tumor abdominal ascites subsided and the very extensive pleural effusion as shown in repeat chest x-rays has completely disappeared.

It is very difficult to accept Rubin's explanation that fluid of this amount in the abdomen and chest can be the result of secretion from the peripheral tumor lymphatics and the forcing of fluid out of the hilar lymphatics in a dermoid of the ovary with fibrosis, size 3 by 2.5 by 2 cm.

Dr. Meigs' observation of the passage of particulate matter into the pleural fluid when introduced into the abdomen in patients having ascites and hydrothorax stimulated us to ascertain the rapidity and amount of transport of radioactivated colloidal gold. Accordingly, a patient with a pelvic liposarcoma of ovarian origin, extensive ascites, and bilateral pleural effusion had 150 mc. of radioactive colloidal gold in 200 c.c. of isotonic saline administered intraperitoneally. Specimens (5 c.c. each) were withdrawn 2, 5, 11, 22, and 34 hours later and finally at the end of 46.5 hours, 1,175 c.c. were withdrawn. The particulate size of colloidal gold is 0.003-0.007 micron. All specimen of fluid withdrawn from the right pleural cavity contained radioactive material. Radioactive material appeared in the pleural fluid as early as two hours after administration. There was a considerable varia-

tion in the concentrations in the specimens. This may be due to the physiological dynamics of the transport mechanism or it may depend on the site of withdrawal or pooling of fluid. On the basis of concentration and volume of fluid withdrawn from the right pleural cavity, it is estimated that 3.5 per cent of gold administered was recovered from the right pleural cavity 46.5 hours later. This experiment supports the experience that Dr. Meigs has had in the case of the transport of India ink from peritoneal to pleural cavities.

Our impression is that abdominal ascites with pleural effusion is more common in the presence of ovarian and uterine pathology not related to ovarian fibromas. Might not the appearance and subsequent disappearance of a hydrothorax following excision of an ovarian fibroma be adequately explained by some mechanism related to the autonomic nervous system?

DR. HENRY L. DARNER, Washington, D. C.—I wish to bring to your attention the importance of the cytologic studies of these fluids when obtained before operation. I bring this to your attention because of a recent experience. An internist had been following a middle-aged patient as having a possible case of recurrent pulmonary tuberculosis because of pleuritic fluid in the left side of the chest. Subsequently, the patient was referred to me. As a result of listening frequently to Dr. Joe Meigs, and finding a freely movable pelvic tumor and fluid in the chest which had not proved to be tubercular, I made a clinical diagnosis of the Meigs' syndrome. At the next chest tapping, in addition to chemical and bacteriologic studies, cytologic studies were done. Paraffin cell pack showed tumor tissue which the pathologist designated as adenocarcinoma. Subsequent exploration proved that the pathologist had made the correct clinical diagnosis for us. The pelvic tumor proved to be an ovarian cystadenocarcinoma.

DR. MEIGS (Closing).—Dr. Kimbrough has raised a very real point, and of course I am cognizant of it just as well as he is. Most thecomas are benign, and a great many granulosa-cell tumors are benign. I included those because most thecomas and granulosa-cell tumors arise from the same differentiating primitive connective tissue. Many thecomas are combinations of thecomas and granulosa-cell tumors, and vice versa. I agree that it might be better to limit the syndrome to fibromas only. On the other hand, it did seem to me that these three groups fitted rather well together. This is all subject to many more discussions and to many more reports.

Smears of the Papanicolaou type were not done on every patient, of course, because some of them date back many years; but on perhaps 12 or 15 patients smears were made, and no evidence of any tumor cells was found in them. I feel that fluid in the chest may occur with a malignant cyst, and although no tumor cells are found the patient might eventually die of carcinoma. That has already happened in two or three of the cases.

I think the syndrome is an interesting one and an important one, and I think it's the kind of thing that we all ought to keep in mind. The fact that a patient has fluid, even bloody fluid, in the chest or the abdomen, or in both, does not necessarily mean she has a malignant lesion. I think it is important to remember that fluid in the chest or abdomen may be caused by a benign lesion, as well as a malignant one.

POSTMENOPAUSAL UTERINE BLEEDING*

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IN MOST reports in the literature the term "postmenopausal bleeding" is used in a broad sense to mean bleeding from the uterus or from any other tissue in the vicinity such as vulva, vagina, urinary tract, or rectum which might simulate uterine bleeding. Bleeding from those sites other than the uterus has little significance in so far as the postmenopausal status of the patient is concerned. Its chief significance is that it may resemble uterine bleeding and must be differentiated from it. *Bleeding from the uterus* is the important symptom in postmenopausal women and to it the term "postmenopausal bleeding" actually applies. However, this term has been used so consistently to mean more than uterine bleeding that we shall employ the more specific term "postmenopausal uterine bleeding" in order to avoid misunderstanding of our remarks.

Postmenopausal uterine bleeding is a resumption of uterine bleeding one or more years after the last menstruation. This implies that, in patients who have such bleeding, the uterus or at least the cervix is present and the ovaries have ceased their function either through physiologic changes, complete radiation castration, or surgical removal.

The choice of one year is preferable to two years after the last menstruation because of the high frequency of cancer in such patients and the urgency of making a prompt diagnosis. It is entirely possible that normal menstruation may occur 12 or 18 months after the last menstrual period, but this is rare. It is more reasonable to submit these few patients to curettage than it is to have a patient with a cancer undiagnosed because of failure to perform a curettage merely because the bleeding had occurred one year rather than two years after the menopause.

This study was made to determine the incidence of malignancy and to evaluate our methods of management.

Material

The patients studied were only those hospitalized either for treatment or for the diagnosis of the cause of the postmenopausal uterine bleeding. The total number of patients so hospitalized was 211. They were consecutive admissions to Passavant Memorial Hospital from July, 1947, to July, 1953. Most were private patients and a few were white clinic patients from the Out-Patient Department of Northwestern University.

*Presented at the Sixty-fourth Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., Sept. 10, 11, and 12, 1953.

Data

The causes of the postmenopausal *uterine* bleeding in the 211 patients are listed in Table I.

The patients were divided into three groups according to the diagnoses: (1) malignancies; (2) benign lesions causing the bleeding; (3) cause of bleeding undetermined. In Group 2 are placed those patients with benign lesions that were considered to be the cause of the bleeding. The patients in Group 3 in some instances had benign lesions but they were not considered to be the cause of the bleeding and accordingly these were not placed in Group 2.

The numerous pathologic lesions found will not be listed since we are not concerned with coincidental pathology but rather have restricted our interest to the causes of the bleeding.

TABLE I. POSTMENOPAUSAL UTERINE BLEEDING
211 PATIENTS

	PATIENTS	PERCENTAGE
Malignant lesions	58	27.5
Benign lesions	72	34.1
Causes not demonstrated	81	38.4
Total	211	100

Group 1. Malignancies

A comparison of the frequency of malignant lesions in this study (Tables I and II) with that in the various published reports is not possible except in one instance because the authors other than Keene and Dunne[1] have not limited their data to postmenopausal *uterine* bleeding. Keene and Dunne[1] in their study of 782 patients found uterine or adnexal malignancies in 59.1 per cent and benign lesions in 40.9 per cent. These figures of malignancies are considerably higher than ours.

TABLE II. MALIGNANCIES ASSOCIATED WITH POSTMENOPAUSAL UTERINE BLEEDING
58 PATIENTS (27.5 PER CENT)

Uterus		53 (91.4%)
Corpus	29	
Adenocarcinoma of endometrium	26	
Squamous and adenocarcinoma of endometrium	1	
Mixed mesenchymal tumor	1	
Sarcoma, fibroid	1	
Cervix	24	
Squamous-cell carcinoma	20	
Adenocarcinoma	4	
Ovary		4 (6.9%)
Papillary cystadenocarcinoma	3	
Granulosa-theca-cell tumor	1	
Tube, papillary adenocarcinoma		1 (1.7%)
Total		58

A comparison should be made with the published data which are not limited to uterine bleeding so that our report can be compared with the broad experience of others. We have thus added to the 211 patients with postmenopausal uterine bleeding the additional 11 patients who were admitted to

the hospital during the same period of time with bleeding from vaginal, vulvar, or urethral causes. The total number then of 222 is comparable to the statistics as presented in the reports in the literature (Table III). To permit a further comparison the cause of bleeding in each of the 222 patients is presented in Table IV.

TABLE III. SUMMARY OF ALL GENITAL MALIGNANCIES IN HOSPITALIZED PATIENTS WITH POSTMENOPAUSAL BLEEDING

AUTHOR	NO. PATIENTS	PERCENTAGE MALIGNANCIES
Zweifel[7]	351	87.0
Geiger[3]	395	81.3
Kanter and Klawans[8]	98	68.4
Schulze[2]	315	68.0
Brown[9]	164	66.8
Taylor and Millen[6]	406	63.3
Geist and Matus[10]	182	57.5
Jones and Cantor[11]	244	54.9
Te Linde[12]	333	53.3
Norris[5]	189	52.9
Fahmy[13]	937	43.1
Schwartz[14]	114	43.1
Benthin[15]	131	42.7
Brewer and Miller	222	26.6
McFadyen[4]	100	16.0
Total	4,181	56.8

TABLE IV. CAUSES OF BLEEDING IN 222 POSTMENOPAUSAL WOMEN* (INCLUDING UTERINE AS WELL AS OTHER CAUSES)

Malignant causes		59 (26.6%)
Carcinoma of endometrium	27	
Mixed mesenchymal tumor	1	
Sarcoma—fibroid	1	
Carcinoma of cervix	24	
Carcinoma of ovary	4	
Carcinoma of tube	1	
Carcinoma of vulva	1	
Benign causes		82 (36.9%)
Polyps	37	
Hyperplasia	11	
Cervical ulcer	10	
Fibroids, submucous or polyp	8	
Endocervicitis	2	
Papillary cystadenoma	1	
Follicular cysts	1	
Vaginitis	5	
Vaginal ulcer	2	
Vaginal endometriosis	1	
Urethral caruncle	1	
Vulvar ulcer	1	
Resumption of menses	2	
Causes undetermined		81 (36.5%)
Total	222	

*This table is comparable to those published in the various reports in the literature on postmenopausal bleeding from all causes.

By either method of considering and reporting the causes of postmenopausal bleeding, the percentage of malignancies obtained in our study is low (27.5 or 26.6 per cent). This may be accounted for in part by the fact that

physicians are hospitalizing more such patients for diagnosis than formerly. Schulze[2] records that 2.2 per cent of 3,310 hospital admissions in one ten-year period were for postmenopausal bleeding, whereas, in the next immediate nine years the percentage had increased to 3.2 per cent. At Passavant Hospital during the period of our study, 4.5 per cent of the total 4,638 admissions to the gynecologic service were for postmenopausal uterine bleeding.

Many years ago the patients hospitalized were predominately those in whom grossly evident lesions were detected during office examination, while in recent years patients are admitted to the hospital for diagnostic procedures irrespective of the presence or absence of positive findings in the office. An example of the latter is had in the study reported here of postmenopausal uterine bleeding: in only 17 of the 211 patients was a positive diagnosis of the cause of bleeding made prior to admission to the hospital and these had malignancies. Thus, 194 patients were admitted for the purpose of establishing a diagnosis.

Certain reports may have a high incidence of cancer because the hospital concerned has an active cancer clinic to which patients are referred, or it may be the type of institution in which patients who have not had medical care and have ignored their abnormal bleeding for a long time but have cancer seek refuge. The report of Geiger[3] from the Cook County Hospital Tumor Clinic of 395 patients with 81.3 per cent malignant lesions seemingly bears out this point. Another feature of his study that suggests this reasoning to be correct is the high incidence of 67 per cent of cervical cancer (265 patients) which is often an obvious lesion, in contrast to the low incidence of endometrial cancer of 8.8 per cent (34 patients) which is usually well hidden until a search discloses it. Such a ratio of 8 cervical cancers to 1 endometrial cancer greatly exceeds the usual ratio in postmenopausal women and suggests a high selectivity. It is generally true and accepted that in postmenopausal patients the incidence of these two types of malignancies is much more nearly equal than during menstrual life. In our institution where patients report promptly after the onset of bleeding and the staff promptly searches for a diagnosis, there were 13.2 per cent (28) endometrial cancers and only 11.4 per cent (24) cervical malignancies. McFadyen[4] reported 14 per cent endometrial carcinomas and 2 per cent cervical malignancies. Norris,[5] in 1935 noted "that after the menopause has been established the relative incidence of fundal carcinoma increases and practically parallels that of the cervix."

Any figure on the incidence of malignancy, even ours limited to uterine bleeding in this report, must be viewed critically and not accepted at face value because many factors need to be considered. While our figures based on postmenopausal *uterine* bleeding are more accurate than those based on a study of patients with vaginal, vulval, and urinary tract bleeding as well as uterine in postmenopausal women, they are deficient to some extent. Some patients still do not seek medical care. Others refuse the advice that a

curettage is necessary. Some of the postmenopausal patients who bleed and who are receiving estrogen therapy are not hospitalized and are accordingly not counted in the statistical analysis.

The figures would be distorted to a greater extent if all patients with bleeding from obvious benign vulvar, vaginal, or urethral lesions were included, but they are not because some are not hospitalized and are, therefore, not included in the compiled data. Examples of such instances are bleeding from a urethral caruncle, a traumatic fissure in the inelastic atrophic tissue of the posterior fourchette, and an acute inflammatory process of the vagina.

That a lower rate of malignancies would be found if all patients were studied rather than only those selected and admitted to the hospital is clearly demonstrated in the report of Taylor and Millen.[6] In their study of 406 postmenopausal patients who were hospitalized, the incidence of malignancy was 63.3 per cent. In contrast to this, the incidence in a group of 291 postmenopausal patients with bleeding treated in office practice was 38.1 per cent.

Thus, the incidence of malignancy as a cause of postmenopausal bleeding must be lower than all the reported figures indicate. It is, however, of such magnitude that the dictum still should be adhered to—that any bleeding in postmenopausal women is indicative of malignancy until it is proved otherwise.

TABLE V. BENIGN LESIONS CAUSING POSTMENOPAUSAL UTERINE BLEEDING
72 PATIENTS (34.1%)

Polyps		37
Endometrial	19	
Endocervical	17	
Endometrial and endocervical	1	
Hyperplasia of endometrium		11
Cervical ulcer		10
Fibroids, submucous or polyp		8
Endocervicitis		1
With cervical stricture		1
Papillary cystadenoma		1
Follicular cyst		1
Resumption of menses		2
Total		72

Group 2. Benign Lesions Causing Postmenopausal Uterine Bleeding

Benign lesions were considered the cause of the uterine bleeding in 72 (34.1 per cent) of the 211 patients (Table V). If a lesion was present but apparently did not cause bleeding, it was placed in the group designated "cause not demonstrated." Fibroids, for example, were found in many patients but in only 8 were they considered the cause of bleeding. In these 8 instances they existed as fibroid polyps within the cavity of the uterus or were in a submucous location.

Polyps were the most common benign lesion associated with bleeding. Hyperplasia of the endometrium was considered a cause, although hormonal factors underlying such tissue changes were probably the primary instigator. That such factors were at play is indicated by the fact that the mucous membrane showed the effect of some estrogenic stimulation in contrast to the

type of atrophic endometrium in postmenopausal patients that is often referred to as postmenopausal hyperplasia. The 10 cervical ulcers were actual ulceration and were not simple cervicitis or erosions. The papillary cystadenoma may not be the actual cause of bleeding since proof is lacking but there remains the often-repeated observation that uterine bleeding is associated with cystadenomas in some patients. It is acknowledged that the bleeding may be purely coincidental.

In two patients in this series the bleeding was undoubtedly a resumption of menstruation, as indicated by the presence of definite menstrual molimen. We feel it is preferable to curette an occasional patient of this type rather than to permit a malignancy to remain undiagnosed.

Group 3. Causes of Bleeding Not Demonstrated

In 81 (38.4 per cent) of the 211 patients no cause for the uterine bleeding could be demonstrated despite the fact that complete examinations were made, including smears, cervical biopsies, and curettage of the endocervix and uterine fundus in those patients with intact uteri or curettage of the endocervix in those in whom supracervical hysterectomies had been previously performed. We realize that it is difficult and sometimes impossible to decide with certainty whether the bleeding is from the uterus or from some other local tissues, but to the best of our ability it was determined by the exclusion of other possibilities that the bleeding originated in this organ. In 18 patients a study of the complete uterus (or cervical stump), tubes, and ovaries which were removed failed to reveal the cause. In two patients the bleeding was profuse from cervical stumps, but no cause was found.

The high incidence of "causes not demonstrated" (38.4 per cent) obtained in this study of postmenopausal *uterine* bleeding greatly exceeds that reported by other authors (0.0 to 8.8 per cent) in studies of bleeding from all causes, some even including hematuria. The explanation for this discrepancy, we believe, rests in the fact that we have excluded many lesions which we feel certain did not cause the bleeding but which other authors have included, apparently only because they were present. Fibroids are a good example. Cervicitis which is listed by many is not considered by us to be a cause except in rare instances. Atrophic endometrium, while listed frequently by others, is not included in our study as a cause per se of the bleeding. In 21 patients no endometrium or only a few isolated glands were obtained at curettage and in another 35 the endometrium was atrophic. Other lesions excluded from our consideration were mesonephric cyst, old healed pelvic inflammatory disease, external endometriosis, and adenomyosis.

It is this group of patients in whom the cause of bleeding was not demonstrated that has induced us to use the term "postmenopausal uterine bleeding, cause undetermined" as a diagnosis. Such usage is consistent with the present-day use of the term "functional uterine bleeding" as a diagnosis. It is a convenient method of signing out hospital records at the time of the patient's discharge and it is excellent for classification of diagnosis and compiling statistical data.

Previous Radiation

In this highly selected group of 211 hospitalized patients with postmenopausal uterine bleeding a study was made of those who had been previously radiated for nonmalignant causes to determine the incidence of uterine malignancies that subsequently developed. Twenty had been so treated. Of these twenty, 5 (25 per cent) later developed carcinoma of the uterus. The remainder of the 211 patients who had not been radiated, therefore, numbered 191. Of these 191 patients, 48 (25.1 per cent) subsequently developed uterine cancer. I presume the most we can say is that in this group of postmenopausal patients who had uterine bleeding the frequency of cancer of the uterus is exactly the same in those who had received radiation previously for benign lesions as it is in those who had received no radiation whatsoever; and that radiation therapy given at a previous date apparently had no effect in altering the frequency of uterine cancer.

Bleeding

The bleeding in the 211 patients consisted of spotting, scant flow, moderate to profuse, or gushing. Spotting and scant flow were the most frequent types in both those with benign and those with malignant lesions.

Gushing bleeding was approximately four times as frequent in patients with uterine malignancies. Thus, in postmenopausal women this type of bleeding strongly suggests malignancy. In women during menstrual life it does also, but the other causes of bleeding of this type, such as retained placental tissue, fibroid polyps, and occasionally functional uterine bleeding, are more frequent, thereby detracting somewhat from the significance of this symptom as an indicator of cancer in women prior to the menopause.

Bleeding after trauma has generally been accepted as indicating malignancy, and this rightfully so, but in this study it occurred just as frequently in patients with bleeding from benign causes. If bleeding from other than uterine causes in postmenopausal women is included, bleeding after trauma is a more frequent symptom of benign lesions because of the frequency of atrophic vulvitis and vaginitis, adhesive vaginitis, and inelastic tissues of the introitus in such patients. This should not detract from the important fact that bleeding after trauma is indicative of malignancy until it is proved otherwise.

To diverge for a moment, it might be mentioned that taking a cervical smear with a wooden applicator for a cytologic smear test produces bleeding from the cervix in almost every instance. It is slight in amount, as a rule, but in some instances it is sufficient to cause one to suspect a malignancy. We attach no significance to it unless there is other evidence of carcinoma. These remarks are made merely to recount our experience and to call attention to the ease with which bleeding from the cervix, even in postmenopausal women, can occur following traumatization with a wooden applicator.

A comparison of the types of bleeding in patients in whom no cause for the bleeding could be found and those in whom it was from identifiable benign

lesions brought out a striking fact, at least astonishing to us. Moderate to profuse bleeding was as frequent in those in whom no cause was found as it was in those with benign lesions. It was also more frequent in patients without malignancies than in those with malignancies.

The duration of time that the uterine bleeding had been present varied considerably. In 13.2 per cent of the patients bleeding from nonmalignant cause, the symptom had endured for one year or more, thus indicating that bleeding of benign origin can endure for a long time. In those with malignancies 29.3 per cent had been bleeding for more than one year before seeking medical attention.

An analysis of the bleeding in the patients with malignancies was made. The character and/or duration of the bleeding did not always reflect the clinical extent of the lesion as one might suppose. Examples are given:

Miss C. G., aged 53 years, 10 years postmenopausal, spotted for one month prior to diagnosis and treatment. She had a Stage III carcinoma of the cervix.

Mrs. P. H., aged 51 years, two years postmenopausal, spotted for three days, four months before diagnosis and treatment. This was the only episode of postmenopausal bleeding and there had been no bleeding during the four months immediately preceding the time the diagnosis was made. She had a Stage III carcinoma of the cervix.

Miss B. S., aged 52 years, 12 years postmenopausal, spotted for one day, one month prior to the curettage. She had an early invasive cervical carcinoma.

Mrs. E. F., aged 65 years, 15 years postmenopausal, spotted for one day, two weeks before she was hospitalized for diagnosis. She had a carcinoma of the endometrium 3 cm. in diameter.

Mrs. M. McD., aged 67 years, 15 years postmenopausal, had a moderate amount of bleeding for two days, one month before she sought medical care. She had a Stage II cervical carcinoma.

Mrs. M. C., aged 57 years, 12 years postmenopausal, had a scant flow for two days and six months later spotted for one day. When examined two weeks later, a Stage I carcinoma of the cervix was found.

Mrs. B. K., aged 54 years, had two short periods of bleeding during her second postmenopausal year; she had passed no blood during the six months immediately prior to the time she was examined. She had a Stage I carcinoma of the cervix.

This brief résumé indicates that in the presence of uterine malignancies the bleeding is often not continuous, may consist of a single episode of spotting, may be intermittent with three or more months between episodes, occasionally may be completely absent for four or six months, and its character or type is not always indicative of the extent of the lesion. From a practical standpoint, then, the occurrence of a single episode of bleeding or of prolonged periods without any bleeding whatsoever does not deny the existence of a uterine malignancy and should not deter one from demanding that a complete study be made, including curettage and cervical biopsies.

Management

The management is predicated upon our concern that a uterine or adnexal cancer is present until proved otherwise in every postmenopausal patient who has uterine bleeding.

At the time of the examination in the office an effort is made to determine whether the bleeding is from the uterus or is from a lesion of the vulva, vagina, rectum, or urinary tract. Interest centers in the uterus because it is by far the most frequent site of malignancies that cause postmenopausal bleeding. In our report, 53 of the 58 malignancies were uterine. This is consistent with other reports.

The history may not be helpful because the patient often can state only that she noted blood on her underclothing or that she observed blood in the toilet after voiding or defecating. A specific question concerning estrogen therapy is always asked since this is now the most frequent cause of postmenopausal bleeding. Such questioning is detailed and persistent. Many patients have been on estrogen therapy so long that they may actually forget they are taking such medication. Even though such therapy is being received it must not be assumed that it is the cause of the bleeding. Seven of the 58 patients with malignancies reported here were on estrogenic therapy at the time of or within three weeks of the time the diagnosis of malignancy was made.

Finding of blood in the vagina is helpful but often the patient is not bleeding at the time of examination. Characteristically, but erroneously, most patients wait until the bleeding ceases before they go to the physician for examination; a regrettable fastidiousness.

An attempt is made to exclude vulvar and vaginal causes by inspection and palpation. Here difficulty may arise because a fissure of the vulva, a vaginitis, or vaginal adhesions may be present and while these might be the cause of the bleeding, they cannot be so designated until uterine and adnexal causes are excluded. For this purpose hospitalization for curettage and cervical biopsies is often required.

Office procedures are limited to smears for cancer, cervical biopsies, and probing of the endocervix. Endometrial biopsies are not taken since a curettage is to be done soon and it is inadvisable to enter the uterus twice within a short period of time because of the hazard of infection. In addition, the endometrial biopsy procedure samples too small a portion of the mucous membrane and cannot be relied upon unless it is positive for cancer. Thus, we prefer curettage as the initial procedure.

Smears for cancer are quite satisfactory in the detection of squamous-cell carcinoma but their reliability is distinctly diminished in the case of adenocarcinoma. In our laboratory the test is accurate in the latter type of malignancy in only 75 per cent in contrast to 95 per cent in epidermoid carcinoma. Thus, this test is used only as a guide. However, it has a practical value as we use it despite its lack of complete accuracy—if a postmenopausal patient has had a little bleeding and a fissure of the posterior fourchette is obviously

the source and if there is no blood in the vagina, the smear, together with clinical judgment, is depended upon to exclude the presence of uterine malignancy. In such cases very few errors will be committed. It is used in a similar manner in those instances in which the bleeding is obviously from a benign vaginal lesion such as a vaginitis. It is admitted that a malignancy of the uterus can coexist with a vaginitis and that both may cause bleeding simultaneously. Even so, too great an error is not made since the bleeding from the vaginal lesion is promptly controlled by appropriate therapy and if additional bleeding continues a curettage is performed. Clinical judgment in such cases also obviates error. For example, a gushing hemorrhage or profuse bleeding would not be ascribed to a vaginal or vulvar lesion which by inspection was totally inadequate to account for such bleeding. If the delay in making a diagnosis can be controlled to a period of two or three weeks, this method is practical and adequate. If there is a question of such control of the patient, immediate curettage is advocated.

A review of our statistics of hospital admissions of postmenopausal patients with bleeding from all uterine, vaginal, vulvar, and urethral meatal causes reveals that only 11, or 4.9 per cent, were hospitalized for differentiation between uterine and nonuterine causes. Most of the patients were hospitalized for investigation and differential diagnosis of the cause of *uterine* bleeding.

The cytologic smear has been used by us up to the present as a means of distinguishing between certain causes of uterine bleeding. It, in conjunction with thorough pelvic examination, is used most frequently to exclude uterine cancer in those patients who are receiving estrogen therapy and are bleeding. At the time the estrogens are discontinued, the smear is taken. If the smear is reported as negative and the bleeding stops, a curettage is not performed but the patient is examined at regular three-month intervals or at any time, if bleeding recurs. If the bleeding does not stop within two or three weeks after withdrawal of the estrogens, a curettage is done at once despite negative smears. This method has seemed suitable despite the fact that cancer can be present and be the cause of bleeding in patients who are receiving estrogens. It has been believed that if cancer was present it would cause the bleeding to continue or to recur in a very short time. From our study of the bleeding in the 58 patients with cancer reported here it is obvious that such reasoning is fallacious. Nine (15.5 per cent) of these 58 patients had not bled for three months prior to the time the diagnosis was made or had had periods of three to six months between bleeding episodes. This makes one pause and reflect on the advisability of withholding curettage in a postmenopausal patient who is bleeding and is receiving estrogenic therapy. On the other hand, from a practical standpoint it does not seem feasible to perform a curettage on all such patients. We have adopted the policy of requiring this procedure immediately for those patients in whom the character or duration of the bleeding seems inconsistent with estrogenic-therapy type of bleeding or in whom suspicious findings are present, such as uterine enlargement. In the other patients the cytologic smear and clinical judgment are depended upon.

Biopsies are taken in the office of all suspicious cervical lesions. They are taken also in all cases at the time the curettage of the endocervix and endometrium is done.

Frozen sections are made during the investigation in some instances but they are not completely reliable, especially in the histologic interpretation of endometrial lesions. Permanent sections are preferred.

Curettage is considered infallible, or nearly so, by many clinicians in establishing the presence or absence of endometrial and endocervical cancer. When the tissues so removed are found to be free of malignant changes on histologic examination they are content to rest their case and draw the conclusion that cancer is not present. We must take exception to this thesis because we are certain that a curettage is subject to error. It may be deficient on two counts: (1) the exploring curette may fail to locate and remove a small endometrial or endocervical carcinoma; (2) the microscopic examination of the curettage specimen may fail to reveal carcinoma even though it is present because all the tissue is not blocked and sectioned, or because the few sections cut from one surface of the block do not include the carcinomatous portion of the tissue. It is impossible to determine the over-all frequency with which curettage fails to reveal carcinoma of the uterus when it is present, but we can state with certainty that in the 52 patients with endometrial or cervical malignancies reported here, curettage failed to reveal the cancer in three instances (approximately 6 per cent, if one dares to express a percentage in such a small series). The details of these 3 patients which are of utmost importance in this presentation are as follows:

1. Mrs. E. A., aged 53 years, 3 years postmenopausal, was admitted to the hospital for curettage on Oct. 7, 1949, because of bleeding. The last menstrual period was in 1946. In May, June, and September of 1949, she spotted blood for a few days. She had been receiving an estrogen continuously for 2 years until Oct. 1, 1949, when it was discontinued.

At curettage a small amount of endometrial tissue was obtained. The uterine canal was distorted by several small submucous fibroids.

Histologic examination revealed atrophic endometrium (Fig. 1) and acute and chronic endometritis.

Follow-up: Estrogen therapy had been resumed by the gynecologist after the curettage and continued until February, 1950, when it was withdrawn. Spotting of blood occurred for 1 day every 6 weeks subsequent to the curettage.

On Dec. 31, 1949, a cytologic smear was negative. Again on March 18, 1950, the smear was negative. Because of continual bleeding after withdrawal of estrogen the patient was hospitalized again.

Second hospital admission: On April 18, 1950, a hysterectomy was performed.

Gross examination: The complete uterus measured 8 by 3.5 by 3.5 cm. and contained numerous small fibroids. The endometrium was 1 mm. thick and the surface was smooth.

Histologic diagnosis: Mixed atrophic and proliferative endometrium (Fig. 2); fibroids.

Additional histologic examination: In one block of endometrium there were reduplications of the glands (Fig. 3); the glands were back to back with scant intervening stroma, and the gland cells varied in size and staining qualities. The nuclei varied in size and stained hyperchromatically. Mitoses were present. Most regions were atrophic.

Diagnosis: Adenocarcinoma of the endometrium, localized.

Without question, the malignancy was present at the time the curettage was performed but its diagnosis was missed by this procedure. With the uterus available for study no malignancy could be identified grossly in the

Fig. 1.

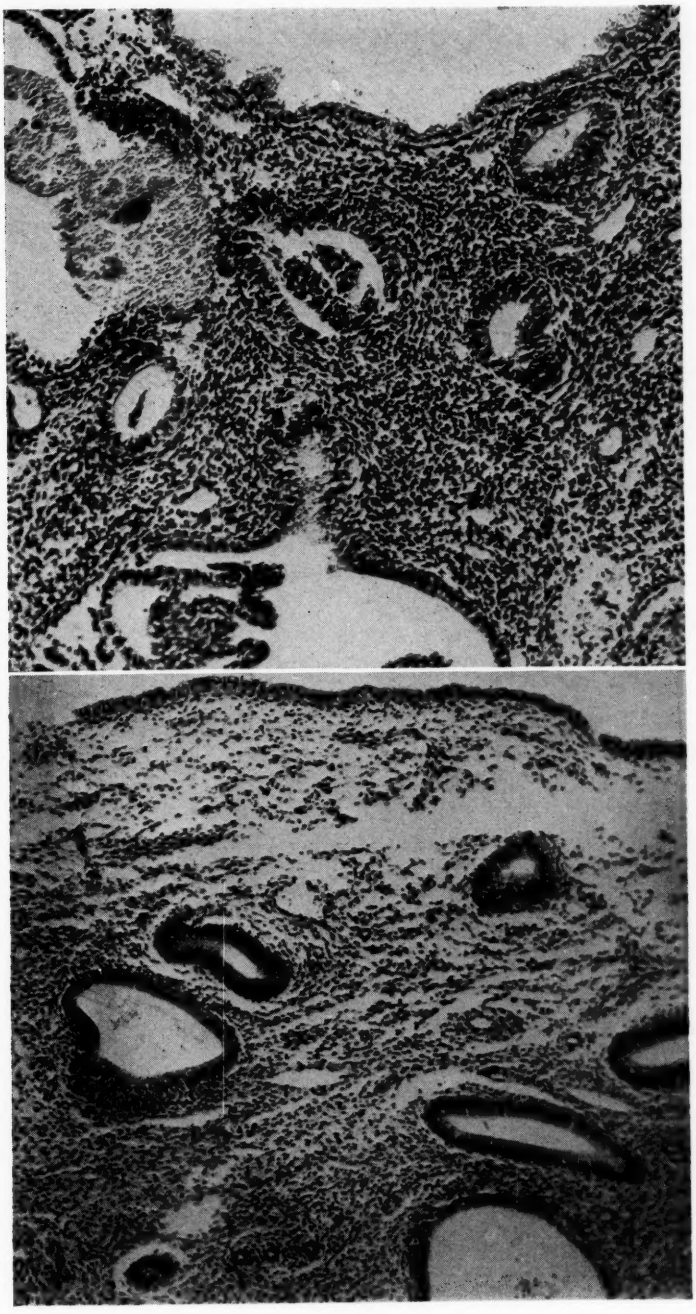


Fig. 2.

Fig. 1.—Patient E. A. Atrophic endometrium obtained by curettage in October, 1949.
Fig. 2.—Same patient as in Fig. 1. Atrophic endometrium in a portion of the uterus removed in April, 1950.

thin, smooth-surfaced endometrium. The histologic diagnosis of carcinoma was not made in one laboratory because the blocks selected for study did not contain the tumor. In the second laboratory the blocks chosen at random included the small tumor and the diagnosis was made. The diagnosis would have been missed again even when the uterus was removed and studied if only one laboratory had made the examination.

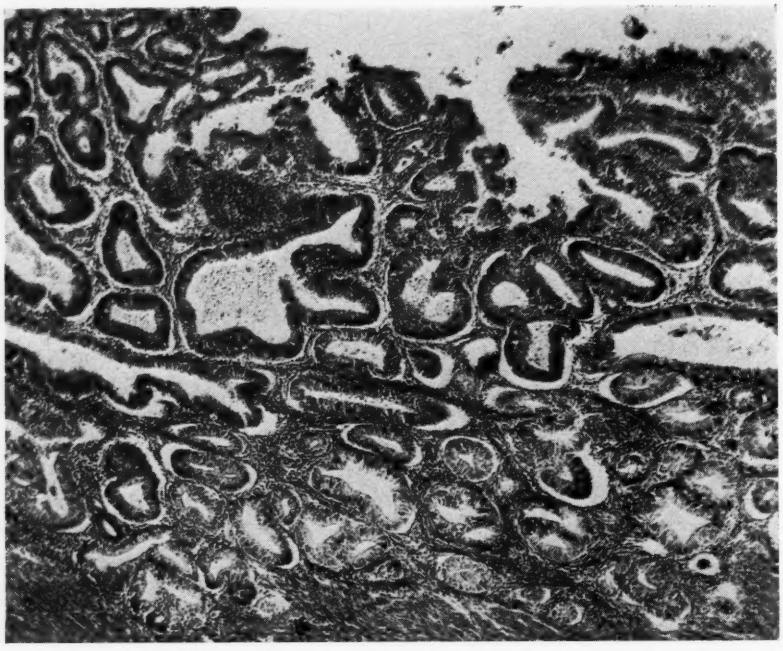


Fig. 3.—Same patient as in Figs. 1 and 2. Adenocarcinoma in a portion of the endometrium adjacent to that shown in Fig. 2.

This second histologic examination was made in the gynecologic pathology laboratory of Northwestern University. Through conjoined effort and agreement between the Departments of Pathology and Gynecology of the University all the gynecological surgical material of two of the hospitals associated with the University are processed first in the Departments of Pathology of the hospitals and then in the gynecologic pathology laboratory at the University. In this manner each specimen receives dual examinations and dual gross and microscopic descriptions and diagnoses. Records and slides are interchanged between the two departments. This double study results in more complete diagnoses since twice the number of blocks, at least, are studied histologically. In most instances many more blocks are studied in our laboratory because of our interest and because we have more time and fewer total specimens to study than does a laboratory of general pathology. The advantages of this dual method of study are exemplified by the above in which the cancer was demonstrated in one laboratory but not in the other. In addition, resident training is provided for both general pathology and gynecologic residents.

2. Mrs. P. B., aged 51, seven years postmenopausal, was admitted to the hospital in May, 1952, for curettage because of bleeding. The last menstrual period was in 1945. In March, 1952, six weeks prior to admission, she spotted blood for 1 week. At this time she was receiving estrogen therapy. A cytosmear was negative.

Fig. 4.

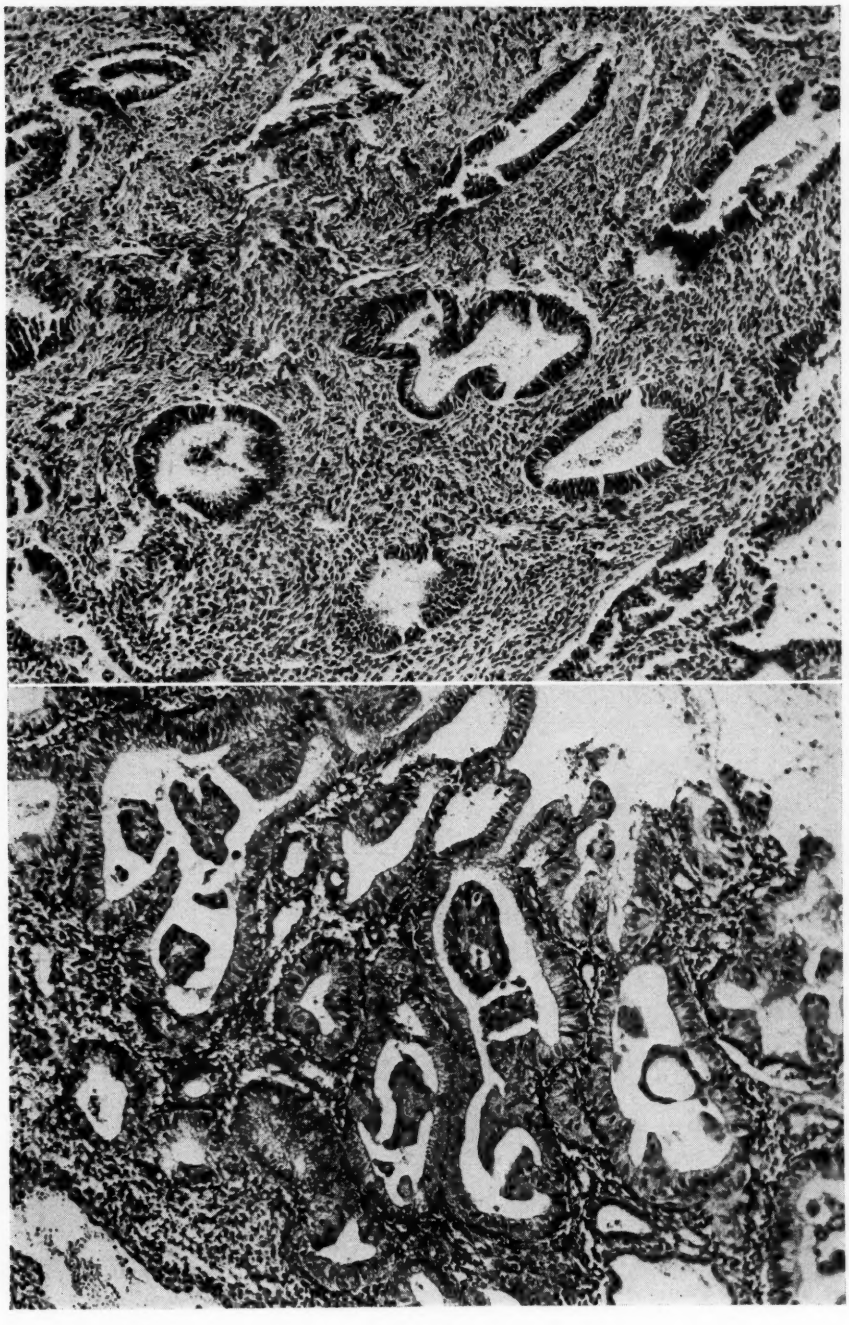


Fig. 5.

Fig. 4.—Patient P. B. Atrophic endometrium obtained by curettage in May, 1952.

Fig. 5.—Same patient as in Fig. 4. Adenocarcinoma in the endometrium obtained by curettage in July, 1953.

At curettage a small amount of endometrial tissue was obtained. A frozen section was negative.

Histologic examination revealed atrophic endometrium (Fig. 4) and normal cervical tissue.

Follow-up: With this evidence that the bleeding was the result of estrogen therapy the gynecologist restarted the estrogenic therapy after the curettage in May, 1952.

Fig. 6.

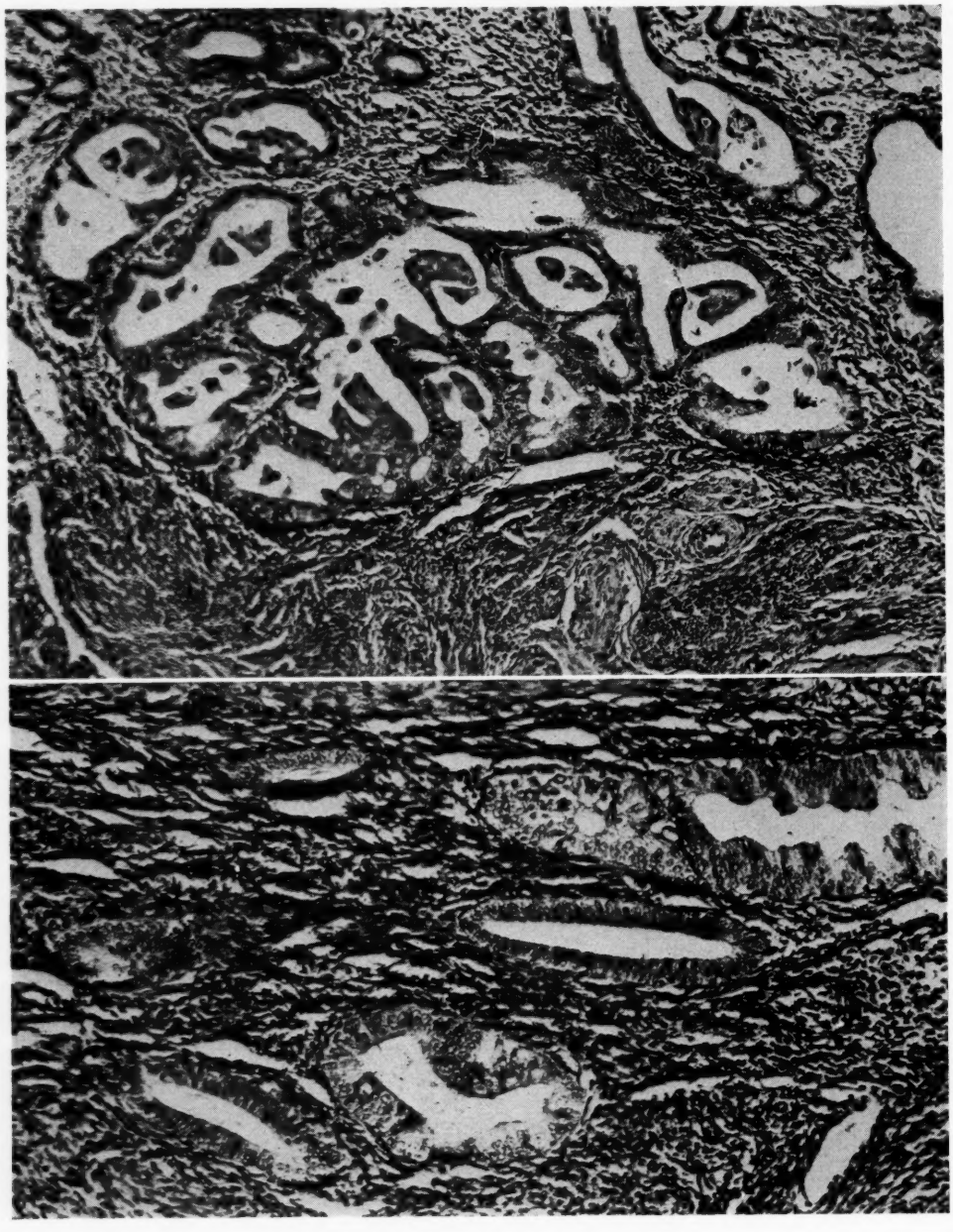


Fig. 7.

Fig. 6.—Same patient as in Figs. 4 and 5. Adenocarcinoma of the endometrium in the uterus removed in August, 1953.

Fig. 7.—Same patient as in Figs. 4, 5, and 6. Higher magnification to show the myometrial invasion.

Fourteen months later (July, 1953) the patient spotted for ten days.

Second hospital admission: On July 28, 1953, a second curettage was done and a small amount of grossly benign endometrium was obtained.

Histologic examination: Adenocarcinoma of endometrium, Grade 1 (Fig. 5).

Third hospital admission: In August, 1953, the uterus and adnexa were removed.

Gross examination: The endometrium was smooth and 0.5 mm. thick. In some regions the gland epithelium consisted of irregular cells with large hyperchromatic nuclei. Papillary projections into the lumen of the glands were numerous (Fig. 6). The myometrium was invaded by nests of these glands in some regions (Fig. 7).

Diagnosis: Adenocarcinoma of the endometrium, invasive.

We assume, and in all probability correctly so, that the carcinoma was present at the time of the first curettage since the symptom of bleeding existed and since the lesion fifteen months later was demonstrated to have invaded the myometrium. It was missed at curettage because of its small size.

3. Mrs. L. B., aged 65 years, 14 years postmenopausal, entered the hospital on Sept. 12, 1947, for curettage because of spotting of blood for several days. A cervical polyp was identified when the patient was examined in the office.

On curettage, meager endometrial tissue was obtained and the polyp was removed.

Histologic diagnosis: Cervical polyp and normal endometrial glands which were few in number and scattered (Fig. 8).

Follow-up: When the patient was next seen on Feb. 16, 1949, she complained of a daily pink discharge for the previous six months.

Second hospital admission: The patient was readmitted to the hospital on Feb. 18, 1949. A curettage revealed grossly malignant endometrial tissue. Radium was applied as a preliminary step in treatment.

Histologic examination revealed endometrial gland cells with mitoses and infiltration of the surrounding stroma. The stroma was scant and compressed (Fig. 9). Cervical tissues were normal.

Diagnosis: Adenocarcinoma of the endometrium.

Third hospital admission: On May 25, 1949, the uterus and adnexa were removed.

Pathology: The blocks of tissue prepared in one laboratory contained residual carcinoma in the myometrium. The blocks prepared in the other laboratory did not contain carcinoma. This again stresses the value of tissue studies in two laboratories whereby more of the total tissue can be studied.

The first curettage demonstrated normal endometrial glands while the second, done 17 months later, revealed endometrial carcinoma that was grossly evident. It is most probable that the malignancy was present at the time of the first curettage and we, accordingly, list this as a deficiency of the procedure.

Curettage may fail to demonstrate sarcoma of the uterus since this malignancy is present most often within a fibroid rather than in the more accessible endometrium. While this lesion occurs infrequently, it is listed as one of the malignancies in most of the reports of postmenopausal bleeding in the literature. In fact, it accounts for 1 per cent of the total malignancies found.

Such instances as these in which the diagnostic procedures are deficient have influenced us in the management of patients with postmenopausal uterine bleeding. In addition, the persistence of bleeding which is alarming and distressing to the patient also brings doubt into the minds of the clinicians

of the accuracy of previous investigations and induces us to be more aggressive in recommending treatment. In weighing the hazards of aggressive major therapy against the hazards of cancer in this group of patients the balance tips heavily in favor of the former. This does not mean that all patients are treated definitively with major procedures, as will be shown, but it does mean that we tend in that direction rather than to performing repeated curettages and relying upon them as the only method of therapy.

A review of the management accorded the 211 patients with postmenopausal uterine bleeding reported here is best made by maintaining the three groupings described before: 58 patients with uterine or adnexal malignancies; 72 with benign lesions as the cause of the bleeding; and 81 with no cause for the bleeding demonstrated.

The 58 patients with malignancies were treated according to our current choice of therapy. Carcinoma of the cervix was treated with radium and roentgen therapy. Carcinoma of the endometrium was treated either with preliminary radium therapy, followed by surgical removal of the pelvic tissues, or by primary surgical procedures without radiation. Ovarian and tubal malignancies were treated surgically.

The 72 patients who had benign lesions which were considered to be the cause of the bleeding were managed in the following manner: Forty patients (55.6 per cent) had diagnostic curettage and cervical biopsies as the complete management since this was thought to be sufficient. The lesions encountered were cervical polyps 17, endometrial polyps 12, endometrial hyperplasia 6, cervical ulcer 4, and cervical stenosis with endocervicitis 1. Only one patient had previously been investigated by dilatation and curettage for bleeding and at that time the findings were the same, namely, cervical stenosis.

In those patients who had endometrial hyperplasia there has been no recurrence of the bleeding and no ovarian tumor has become evident.

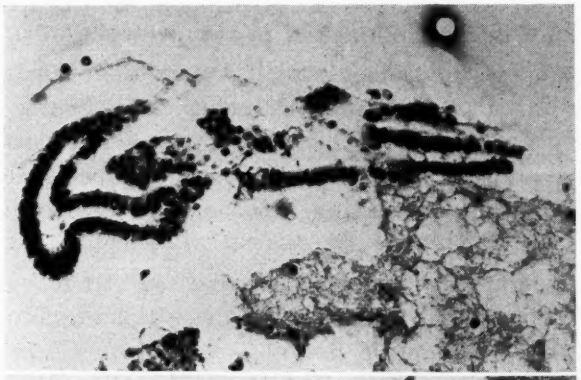
Thirty-two patients (44.4 per cent) were treated definitively by surgical procedures or radiation. Only 4 had had curettages performed at some time previously. Thus, the majority were treated initially with definitive procedures. Twenty-six had hysterectomies or removal of the cervical stump in those cases in which the uterus had been removed previously. Six were treated by insertion of radium into the uterine canal.

The indication for the surgical procedures in the 26 patients operated upon was either the presence of the benign lesion which was believed to cause the bleeding or was this factor plus the presence of a coexisting lesion or lesions that in themselves required such therapy. Examples of the first one are: (1) a large fibroid polyp, (2) a cervical stenosis and hematometra, (3) a cystadenoma. Examples of the second are: (1) symptomatic cystourethrocele and submucous fibroids, (2) uterine prolapse and cervical ulcer.

The lesions encountered in the individual 26 patients were: fibroids (polypoid or submucous) with vaginal relaxation 2, without relaxation 7; endometrial polyps with vaginal relaxation 4, without relaxation 2; cervical ulcer with relaxation 4, without relaxation 1; ovarian cysts 2; endometrial hyperplasia 3; and cervical stricture 1.

Curettage immediately prior to the operative procedure prevents operating upon and performing an inadequate procedure in patients with a previously unrecognized carcinoma of the cervix. A curettage is dispensed with

Fig. 8.



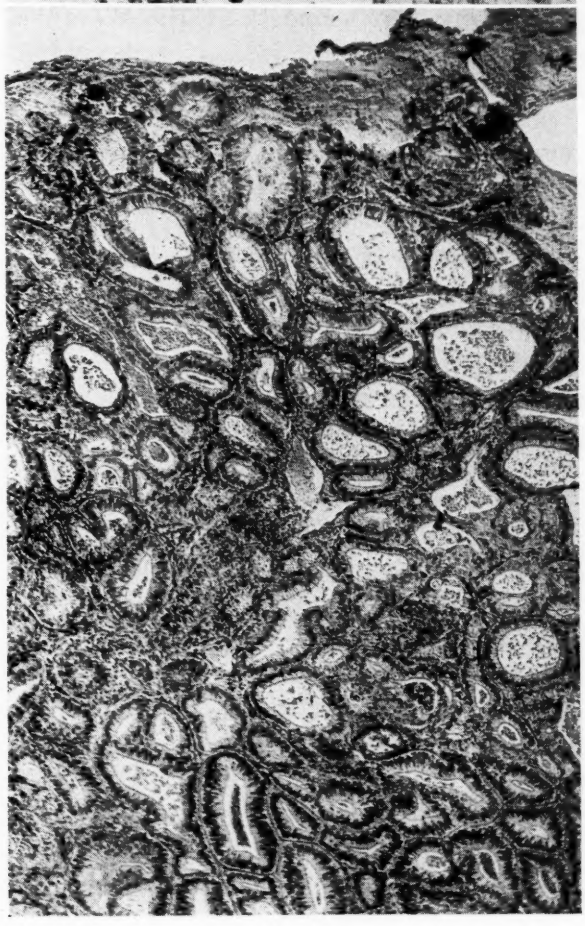


Fig. 9.

Fig. 8.—Patient L. B. Atrophic endometrial gland obtained by curettage in September. 1947. The total amount of tissue obtained by curettage was extremely meager.

Fig. 9.—Same patient as in Fig. 8. Adenocarcinoma of the endometrium obtained by curettage in February, 1949.

when a patient with uterine bleeding has an ovarian tumor if cancer of the cervix has been excluded by adequate biopsies of the portio and endocervix. A smear might be helpful since it might provide a diagnosis if a biopsy should miss a small lesion. If such a patient had an endometrial carcinoma, the primary procedure would be surgical without preliminary radiation in any respect since radium is contraindicated in the presence of an ovarian tumor.

In some instances the lesions which are present and require surgical therapy but have no part to play in producing the bleeding may provide the opportunity to remove the uterus. This is fortunate since the bleeding can be terminated once and for all, its serious complications can be dismissed, and the needed correction of a coexisting lesion can be accomplished by one procedure.

Six patients received radium at the time of curettage. In four the endometrial tissue obtained upon curettage was grossly malignant and the radium was given with the presumptive diagnosis of cancer. Frozen sections are not always reliable and in a few instances such as these the therapy is given before the permanent sections are studied. If such study reveals no malignancy, the radium can be removed before the dosage reaches the minimal amount given for cancer. While there is no great objection to such a method of management our choice procedure would be hysterectomy rather than radium if malignancy could be excluded with certainty. We prefer to accomplish the treatment with one procedure rather than do the curettage, wait 48 hours for permanent sections, and then either give radiation therapy or perform a hysterectomy. It is less hazardous to perform the entire procedure at the time of the curettage.

The other two patients received radiation to control bleeding of nonmalignant origin. Its use under such circumstances is restricted as indicated by the fact that only two patients were so managed. We personally prefer surgery to radiation in the treatment of benign pelvic lesions.

The 81 patients in whom no cause for the bleeding was demonstrated were managed as follows: 57 patients (70.4 per cent) were managed by curettage and cervical biopsies. No additional therapy was given. Six of these patients had had 1 to 3 curettages previously. Twenty-four patients (29.6 per cent) were treated definitively with radiation therapy or by surgical procedures. Two of these had been curetted previously. Five patients were radiated at the time of curettage; one was thought to have endometrial carcinoma as determined by inspection of the curettings grossly (subsequent microscopic examination demonstrated this to be in error); the other 4 patients received radiation therapy for bleeding from some benign unknown cause. There are occasional contraindications to surgical procedures in an older age group of patients such as reported here and radium under such circumstances is a suitable medium of treatment. However, we prefer hysterectomy whenever possible in older patients.

The remaining 19 patients were treated surgically by hysterectomy or removal of the cervical stump. Nine of the 19 patients had cervical stumps

which were removed. This latter is an extremely high percentage but it reflects our idea of the best management of postmenopausal bleeding from such a cervix.

Bleeding from stumps concerns us more than bleeding from a postmenopausal endometrium and we strongly favor surgical removal at the time of the first investigation if cancer can be excluded. The indications for the surgical removal of the stumps were bleeding, alone, in 5 instances; persistent leukorrhea and bleeding in 1; bleeding plus pelvic pain on motion of the stump 1; and 2 were removed for bleeding at the time a symptomatic cystourethrocele was repaired.

The indications for hysterectomy in the remainder of the patients in this group were bleeding, alone, in 3 instances and in 6 patients the bleeding uterus was removed in conjunction with surgical repairs for symptomatic vaginal relaxations. In one patient a cervical amputation for biopsy purposes was done at the time of curettage.

Two of these 24 patients treated definitively with radium had had a curettage previously. The treatment was thus given at the time of the first curettage in the majority of instances. This reflects our preference for immediate definitive treatment even in patients in whom no cause for the bleeding is apparent. Nevertheless, a review of the 57 patients who had only curettage shows that 6 of these had had 1 to 3 curettements previously. This shows that while we prefer immediate definitive treatment, we do subscribe to the principle that repeated curettage is a suitable method of management in a few patients. Our general rule, however, is that a curettage may be done without being followed at once by definitive treatment but that a second curettage done for recurrence or persistence of the bleeding should, in most instances, be accompanied by definitive therapy.

Summary

The incidence of uterine or adnexal malignancies in the 211 patients with postmenopausal *uterine* bleeding was 27.5 per cent (58 patients). It is low because our current practice of hospitalizing most patients with postmenopausal uterine bleeding has increased the total number of patients to a greater extent than it has the number of patients with cancer.

Benign lesions were the cause of, or were involved in the production of the bleeding in 72 (34.1 per cent) of the 211 patients.

The cause of the bleeding could not be demonstrated in 81 (38.4 per cent) of the 211 patients. This is a greater incidence than recorded in most reports because we exclude as causes such pathologic findings as chronic cervicitis (diagnosed histologically), adenomyosis, atrophic endometrium, and some fibroids.

A single episode of spotting for 2 days, 2 or 3 months before the patient is examined, may indicate the presence of cancer. Postmenopausal patients with cancer may have no bleeding at all for 3 to 6 months between episodes or after a single episode of uterine bleeding. This occurred in 9 of the 58

patients with cancer reported here. The longest period without flow was 6 months. This happened in 2 of the 9 patients. The conclusion drawn is that even though the bleeding occurs several months prior to the time the patient reports to her physician, it must be considered to be indicative of cancer until it is proved otherwise.

The quantity, duration, or character of the bleeding neither indicates accurately the extent of the cancer nor provides a means of distinguishing malignant from benign lesions.

Curettage is not infallible although it is so considered by many clinicians. In 3 of the 52 patients with uterine cancer curettage failed to provide the diagnosis and caused a delay of 6, 14, and 17 months, respectively, in the recognition of the endometrial carcinomas.

In the management of postmenopausal uterine bleeding curettage should always be performed. It is considered adequate therapy in many instances. In our study 97 (63.4 per cent) of the 153 patients in whom the bleeding was from nonmalignant cause were so treated. This procedure should always be accompanied by curettage of the endocervix and multiple cervical biopsies. It is important that such patients have follow-up examinations, since postmenopausal patients with uterine cancer may have no bleeding for periods of 3 to 6 months, and since curettage and cytosmears are not completely reliable.

Definitive procedures (hysterectomy or radiation) are carried out at the time of the curettage whenever feasible. This is desired because the incidence of cancer is high in patients with postmenopausal bleeding, and because it is known that the diagnostic procedures are subject to error. Of the 153 patients with bleeding from benign causes, 56 (36.6 per cent) were treated definitively. Fifty of these were so treated at the time of the curettage. Often there are coexisting lesions that require surgical management, such as vaginal relaxation, which provides the opportunity to extend the procedure to include removal of the pelvic organs. In other instances, bleeding alone is an adequate indication for consummation of definitive measures. Of these 56 patients, definitive treatment was carried out in 12 for the indication of bleeding only.

We prefer surgical procedures to radiation in the treatment of patients with postmenopausal uterine bleeding from nonmalignant causes. Radiation is reserved for the treatment of malignancies. It is used in benign conditions only when there are contraindications to surgical procedures. Our preference of surgical procedures is vaginal hysterectomy but in the past we have not always removed the tubes and ovaries if they were atrophic and free of tumor and if the procedure was unusually difficult. We are now convinced that they must be removed when a hysterectomy is performed in a patient with postmenopausal uterine bleeding. If this cannot be accomplished readily vaginally, either a combined vaginal and abdominal procedure should be performed or the abdominal approach should be selected initially.

If bleeding continues or recurs after a diagnostic curettage is performed, a second curettement is indicated. At the same time, if the bleeding is determined to be from a benign cause, definitive treatment is given. This is done unless there is some contraindication.

Curettage, repeated at intervals, does not constitute the best management of continued or recurrent postmenopausal uterine bleeding.

References

1. Keene, F. E., and Dunne, F. S.: Pennsylvania M. J. **41**: 503, 1938.
2. Schulze, M.: California & West. Med. **39**: 158, 1933.
3. Geiger, C. J.: Illinois M. J. **80**: 406, 1941.
4. McFadyen, E. H.: AM. J. OBST. & GYNEC. **63**: 178, 1952.
5. Norris, C. C.: Internat. Clin. **1**: 182, 1935.
6. Taylor, H., and Millen, R.: AM. J. OBST. & GYNEC. **36**: 22, 1938.
7. Zweifel, E.: Deutsche med. Wchnschr. **56**: 1388, 1930.
8. Kanter, A. E., and Klawans, A. H.: AM. J. OBST. & GYNEC. **24**: 192, 1932.
9. Brown, P. T.: J. Iowa M. Soc. **23**: 261, 1933.
10. Geist, S. H., and Matus, M.: AM. J. OBST. & GYNEC. **25**: 388, 1933.
11. Jones, B. D., and Cantor, E. B.: AM. J. OBST. & GYNEC. **62**: 365, 1951.
12. Te Linde, R. W.: Am. J. Surg. **48**: 289, 1940.
13. Fahmy, E. C.: J. Obst. & Gynaec. Brit. Emp. **40**: 506, 1933.
14. Schwartz, R. M.: AM. J. OBST. & GYNEC. **45**: 522, 1943.
15. Benthin, W.: Arch. f. Gynäk. **132**: 86, 1927.

Discussion

DR. ANDREW A. MARCHETTI, Washington, D. C.—First of all, the authors should be commended for expressing the desirability of restricting the definition of postmenopausal bleeding to the uterus.

In their analysis it is shown that among the 222 patients who were hospitalized for postmenopausal bleeding, in 211 instances, or approximately 95 per cent of them, the source of the bleeding, whether the cause was determined or undetermined, was uterine. Their thesis emphasizes that, even though in the remaining 5 per cent of the cases the bleeding came from the vulva, vagina, or urethra, it must not be assumed at once that the uterus can be excluded as the site of a dangerous lesion.

Postmenopausal uterine bleeding is defined as a resumption of uterine bleeding one or more years after the last menstruation, preferably one year according to their choice. I can readily accept this definition and can happily agree with the choice of the specific time limitation. However, it is a little difficult for me to accept the implication that the ovaries have ceased their function through physiologic changes in patients with postmenopausal uterine bleeding 12 or 18 months after the last menstruation. Some justification, it appears to me, is added to this slight protest when the authors themselves state that although it is rare "it is entirely possible that normal menstruation may occur 12 or 18 months after the last menstrual period." As one who is ever conscious of ovarian function and its implications, I would substitute the word "altered" for the word "ceased" under the special circumstances mentioned.

It is encouraging, though a little surprising, that the incidence of malignancy in their survey was between 26 and 28 per cent. Their commentary on this low incidence is laudable for they especially point out that it should not mislead anyone. In comparison with other similar analyses it is low, but in so far as cancer is concerned it is still relatively high and it definitely means that under any circumstance postmenopausal uterine bleeding is cancer until proved to the contrary.

Of the three categories into which the authors divided their patients, I should like to ask Dr. Brewer a question about the third category, that is, the group in which the causes of the bleeding were not determined. This group constituted 36.5 per cent of the series. In the first two groups there were anatomic lesions to cause the bleeding. I got the impression that the group with causes undetermined is synonymous with the group

that others would place under functional bleeding. Was there any attempt made to find a systemic cause for the bleeding among those patients? One occasionally hears of postmenopausal uterine bleeding associated with hypertensive disease, for instance.

The observations that the authors made on the types of bleeding and the time intervals between episodes of bleeding were interesting. I do not believe that one has much difficulty in understanding the mechanics of bleeding caused by anatomic lesions and the part that necrosis and infection play in this mechanism. On the other hand, the initiation and the mechanics of functional bleeding are still not clearly understood. On that basis, no direct correlation can be made from the authors' interesting observations. One can conclude, however, that postmenopausal uterine bleeding is an abnormal manifestation in any case and the more insignificant it is, the more is it mandatory to rule out malignancy.

The management of postmenopausal uterine bleeding as it was described and evaluated by the authors leaves little for disagreement as far as I am concerned. I am in accord and heartily endorse the basic principles governing their management.

DR. DANIEL G. MORTON, Los Angeles, Calif.—I would like to comment upon five points in Dr. Brewer's study.

1. From the statistical viewpoint much depends upon definition. Picking one year after the cessation of menstruation as the starting point suggests to me that a good many of the undiagnosed bleedings were, in fact, last gasps of menstrual function. This is a confusing age period—undoubtedly some estrogenic effects persist for a considerable time after the cessation of more or less definite periodic bleeding, due presumably to the ebb and flow of more or less definite (and substantial) amounts of estrogen. Even at two years after cessation of periodic bleeding we may occasionally have return of bleeding because of the further ebbing of estrogenic titer. It is not suggested that such facts should change the management of such cases, but only that the percentages of the three categories are dependent upon the definition of postmenopausal bleeding employed.

2. I like the balanced program of management suggested, yet feel that, except in the case of the prior and extensive use of estrogenic substances where some delay in curettage often seems to be indicated, until or unless bleeding recurs in the absence of estrogenic therapy, postponement of curettage is dangerous on the assumption that one has control of the patient and that she will return as advised. I have been fooled in this regard and no longer take the chance.

3. I like Dr. Brewer's choice of definitive therapy, usually hysterectomy, if the solution to the problem has not been achieved by the first curettage. Rarely does the postmenopausal woman have a return of bleeding after curettage unless some important pathological process exists. We are all aware of the possibilities of missing cancer of the endometrium by curettage, particularly if it is a small lesion in a small postmenopausal uterus. This brings me to the fourth point:

4. The technique of curettage is too frequently faulty. I am aware that many men use only the curette and do not follow it up with the use of some sort of grasping forceps, such as a small ovum forceps. This omission frequently results in the missing of certain of the intrauterine lesions, the polyp, for example. In the last two years I have seen four unnecessary hysterectomies performed because of this error in technique. I think that it is an important point.

5. The last point upon which I would like to comment briefly is the use of the vaginal smear as an aid in the study of such patients. It is my belief that this is a valuable measure, even though for endometrial lesions the percentage of accuracy is far below that for cervical cancer. It appears to me that the vaginal smear is gradually finding its place in our diagnostic armamentarium—and it is an important place. It would be of interest to know how often the smear was responsible for the diagnosis in this series of cases.

DR. RICHARD TE LINDE, Baltimore, Md.—Dr. Brewer has given a very thoughtful analysis of this one symptom, which I think is one of the most important symptoms with which we deal in gynecology. About 20 years ago I made a similar study, and I think it's important that these studies be made from time to time, because changing factors alter the figures from year to year. For instance, our percentage of malignancy was 53, in contrast to Dr. Brewer's 26. I think the two main factors in changing these figures have been (1) the fact that physicians are more alert to this symptom and send their patients in sooner, and (2) the increasing use of estrogen therapy, which is now the greatest single cause of postmenopausal bleeding.

I agree with Dr. Brewer in setting one year from the date of the last period as the arbitrary time to consider bleeding postmenopausal; you have to be arbitrary at some time, and I think one year is the sensible limit. We all know, however, that ovulation can take place much later than that, and we have one proved case in which ovulation and menstruation took place five years after the last previous period in a 55-year-old woman. As proof, we have the uterus and the corpus luteum for study.

I found in our cases that even in the best years of carcinoma of the endometrium—that is, postmenopausally—carcinoma of the cervix was about twice as common as carcinoma of the endometrium, which apparently is different from Dr. Brewer's finding.

I would like to back up with a slide what has just been said by Dr. Dan Morton. We independently have come to the same conclusion, apparently, that he has, that a curette is not the only instrument that should be used in doing a curettage. This is a very recent case. In the picture you will see all the tissue that I could get after doing a very thorough curettage under anesthesia. Then I used a small forceps, which actually is a ureteral stone forceps that Dr. Kelly left us many years ago, and with the first attempt with the forceps I pulled out the large endometrial polyp which you see in the picture. That happens to be a benign polyp, but I have done the same thing in the case of a polypoid endometrial malignancy. So that a forceps is placed on the table every time we do a curettage, and we use it routinely.

I have one minute remaining in which I would like to disagree with my good friend from Chicago. Thirty-six per cent of the cases showing benign lesions were given definitive treatment, which in his clinic usually means vaginal hysterectomy. The most common lesion responsible for the bleeding found in this group was a cervical polyp—a lesion that can be quite satisfactorily and safely removed in any gynecologist's office. The second most common lesion found was an endometrial polyp, which could have been removed by curette or by the small forceps which I have just shown you. I submit that the performance of a hysterectomy for these minor benign lesions is not justifiable major surgery. Whenever I remove a bleeding uterus—as I have done—and find only a benign endometrial polyp, I consider that I have made an error.

Dr. Brewer removed the uterus in 26 per cent of those cases in which no gross or microscopic lesion was found to explain the bleeding. In my opinion many of these patients would have had no recurrence of the bleeding if nothing more had been done. If the bleeding recurs in such cases, we perform another curettage. We prefer to know the exact pathology before resorting to definitive treatment. After all, if endometrial cancer has been overlooked, a vaginal hysterectomy is not the correct treatment; and if no malignancy exists, such major surgery is seldom necessary.

DR. FRANK R. SMITH, New York, N. Y.—At Memorial in years past we have treated many of these patients incorrectly by the insertion of radium after curettage. Many of them merely had a fibrosis of the uterus to which we simply added more fibrosis.

In an attempt in 1947 to see whether the incidence of cancer of the endometrium was greater after a previous curettage, Dr. Lemuel Bowden and I reviewed about 1,000 cases in which curettage and irradiation had been done during the period from 1926 to 1936. In that group we insisted that at least 10 years must have elapsed from the time of the insertion of the radium, and that we must have the original curettings for review.

We collected 35 cases out of about 900 which had been previously treated by curettage and irradiation for benign lesions. We discarded all but 8, either because we couldn't get the curettings or because the patient had had recurrences within two to four or five years.

The thing on which we agreed very much with Dr. Brewer is that two-thirds of our patients with nonmalignant lesions were cured by curettage alone. Of the remaining third there were only 10 per cent who had endometrial carcinomas. We found endocervical cancer in about 5 per cent.

DR. LEROY CALKINS, Kansas City, Kan.—Using a somewhat more restricted group even than that used by Dr. Brewer, namely, patients with uterine bleeding who have no positive findings on pelvic examination, and no blood coming from the cervix on reexamination with the speculum after rather vigorous uterine palpation—we found in 200 consecutive patients 40 endometrial carcinomas. Naturally, we found very few cervical carcinomas under those circumstances, but 20 per cent had endometrial carcinomas. I think that is an extremely important item for us to teach our students and house officers.

DR. HOUSTON EVERETT, Baltimore, Md.—I have had one case that bears on this subject which was so frightening that I think it is worth reporting. This patient was a woman in her sixties with a profound cancerphobia, who complained of a sticky, slightly pinkish discharge of about six weeks' duration. She was very difficult to examine because of a very small vagina, but on speculum examination she did appear to have a senile vaginitis, for you could see blood oozing from the vaginal walls.

To be on the safe side, however, we curetted her and biopsied the cervix. There was no tissue from the curettage, and the cervical biopsy was negative. This was in April, 1951. The uterus at that time felt normal in size for a postmenopausal uterus, and it was of normal depth. In July of that year she was operated on in Richmond for a sarcoma of the uterus, said to be as large as a grapefruit. I still don't know how we could have made that diagnosis in April. Because of that frightening experience, I recently operated on a 65-year-old lady with profuse uterine hemorrhage in whom curettage and biopsy yielded nothing. A hysterectomy was done abdominally, because the vagina was almost too small even for the curettage. The specimen showed several fibroids, small ones, one of which was submucous and ulcerated and was the cause of her bleeding.

DR. T. C. PEIGHTAL, New York, N. Y.—Our diagnostic efforts in this regard closely parallel those which Dr. Brewer has outlined for us. I would like to emphasize certain observations from his thesis with which our experience is in agreement. The majority of our cases of bleeding were due to endocrine therapy. Less than one-third were malignant and two-thirds were benign or of undetermined cause. Neither the time from the onset of the bleeding symptom, nor the duration of a given episode, nor the repetition of its occurrence gave any reliable clue to the benignancy or the malignity of its cause. Polyps, cervical or endometrial, were the cause in approximately 50 per cent of the benign cases. In the therapy of the benign group, Dr. Brewer has shown rare judgment in deciding when to be satisfied with curettage and biopsy alone and when to remove the uterus or the remaining stump of the cervix.

We would like to draw your attention particularly to the statement that cytological smears were accurate in only 75 per cent of the fundal but in 95 per cent of the cervical lesions—a finding to which Dr. Morton also has alluded. Our reason for so doing is to mention a diagnostic procedure which has helped us greatly in obtaining better smear preparations from these patients with postmenopausal bleeding and discharge.

After taking the usual suction smear from the canal of the cervix and a smear by spatula scraping from the os of the cervix with negative results, a third specimen is obtained by fitting a plastic suction cup over the cervix for 12 to 24 hours and then examining its contents by the smear technique. By this method we have picked up two

cases of early fundal malignancy not found in the usual manner of smear taking, and have picked up also one case of tubal carcinoma in which this procedure was especially helpful.

In the latter the first smears were positive for adenocarcinoma cells. A curettage and ring biopsy of the cervix were done, sections from which proved negative histologically. Pelvic examination revealed a normal-sized uterus and adnexa. The patient's bloody discharge persisted even after enough time had elapsed to heal the effects of biopsy and curettage, and another cap smear specimen was again positive for adenocarcinoma type of cells. Feeling as certain as one can that we had done a thorough curettage from which the whole block was sectioned and proved negative, we assumed that the cells must be tubal, and were rewarded on exploration in finding a left hydrosalpinx and a soft clubbed right tube filled with a well-contained cancer within the lumen. We feel that the cap smear technique helped immeasurably in leading us to this early lesion.

DR. BREWER (Closing).—I must admit that I remove rather promptly the uterus that is bleeding in a postmenopausal patient, especially if there are other indications for a surgical procedure such as relaxations. In the absence of such indications the uterus is removed in a certain percentage, as indicated in the presented statistics. These same statistics indicate that we do not remove all or even a majority of such uteri. Hysterectomy is favored after the second curettage with negative findings because of the high frequency of cancer, the possibility of error in the diagnostic procedures, and the firm belief that curettage repeated at intervals is not the procedure of choice in the management of patients with postmenopausal uterine bleeding.

Dr. Marchetti's suggestion of change in the definition is perfectly acceptable. The idea we had was to attempt to exclude from a postmenopausal classification those patients who had had hysterectomies but still had functioning ovaries. Since they do not menstruate they might be considered postmenopausal, according to the strict meaning of the word as given in the dictionary; but they are not, because normal and regular ovarian function is still present. To exclude them, a rather long and restricted definition was given.

The forceps utilized by Te Linde are excellent, and their use by us might well have provided a few more diagnoses of the cause of the bleeding.

The patient who caused this study to be started was one who had been curetted four times with negative findings. Six months after the fourth curettage she bled again, and it was believed by her doctor that she need not be hospitalized again because she had already had four curettages. Just the day before I came to this meeting we had a follow-up on her which will change all my statistics. One month ago she died of an inoperable carcinoma of the ovary. Had we treated her according to our plan, she would not have had four curettages without definite treatment and she would not have died of a genital cancer.

May I repeat that the ovaries should be removed along with the uterus whenever surgery is performed in these patients, and if this cannot be accomplished vaginally the abdominal approach should be utilized.

CARCINOMA OF THE BODY OF THE UTERUS*

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THIS paper presents a study of endometrial cancer based on the observation of 421 patients who have been seen in the gynecological clinics of the Department of Obstetrics and Gynaecology of the Toronto General Hospital, and in the Ontario Institute of Radiotherapy at that hospital, from 1937 to 1952. The two clinics are complementary one to the other and, because of their nature, they attract patients of varying types. First, there are those who present themselves initially for diagnosis and whose treatment is entirely under our control; second, there are those who are referred for postoperative radiotherapy after surgical treatment elsewhere; and, third, those whose general condition or the extent of their disease when they present themselves to us for treatment precludes the hope of successful surgery. Taken as a whole, the group of patients presents a broad field for a consideration of the problems of endometrial cancer. The patients have all been under regular observation at the follow-up clinic for cancer patients, and the records have been maintained in the Tumour Registry of the hospital.

In our experience, cancer of the corpus occurs eleven years later than cancer of the cervix. The average age of the patients has been 59 years, the youngest being 26 and the oldest 90 years of age. The greatest number have been in the decade from 55 to 64 years of age (Table I).

Table I. Distribution by Age Group
1937-1952

AGE	NUMBER OF CASES
Under 30 years	1
30-34 years	4
35-39 years	6
40-44 years	17
45-49 years	45
50-54 years	52
55-59 years	90
60-64 years	87
65-69 years	56
70-74 years	37
75-79 years	18
80 years and over	8
Total	421
Average age—59.2 years	

*Presented at the Sixty-fourth Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., Sept. 10, 11, and 12, 1953.

It is generally accepted that there is a type of woman who is prone to develop cancer of the endometrium. The features which mark her not only suggest a possible endocrine imbalance, but also sometimes mask the diagnosis of malignancy, and often increase the risk of surgical treatment. The patient is large and obese, hypertensive, and has a greater than average tendency to be diabetic. She is relatively sterile and often her uterus is distorted by fibroids. She frequently has a late menopause which is often preceded by menorrhagia. An analysis of these characteristics among the cases under consideration shows that they conform in a general way to this pattern (Table II). We have noted also among them frequent late menarche, but reliable information is available in so few cases that this cannot yet be accepted as necessarily a dominant feature.

TABLE II. CLINICAL FEATURES

CALCULATIONS BASED ON NUMBER OF CASES IN WHICH RELIABLE INFORMATION IS AVAILABLE 1937-1952

CLINICAL FEATURE	NO. OF CASES	%
Obesity	387	46.0
Hypertension	421	18.5
Obesity and hypertension	387	12.7
Diabetes	421	4.7
Nulliparity	395	35.9
Incidence of fibroids	421	25.0
Delayed menopause (52 years or over)	346	21.0

It is often very difficult to determine the extent of the lesion in endometrial cancer. The combination of a heavy abdominal wall and a small or virginal vagina makes a satisfactory examination impossible, so that the size of the uterus, the degree of its mobility, and the presence of extrauterine masses may not be determined until operation is undertaken and the abdomen is opened. For this reason we have not attempted to divide our cases by stages and have adopted the simple classification proposed by Heyman[1] many years ago—operable, technically operable, and inoperable. On this basis every patient is considered as a potential surgical problem and treatment prescribed accordingly, with the realization, at the same time, that conditions may be present which may alter the initial classification of the case.

The surgical treatment of the patients at the Toronto General Hospital is shared by all members of the gynecological staff, and a large proportion of the patients are operated upon by the resident gynecologists. Therefore, although we are attempting to follow a planned routine of treatment—intracavitary radium followed in about six weeks by total hysterectomy and bilateral salpingo-oophorectomy—in the earlier years especially, some members of the staff did not choose to follow this procedure.

As a rule the regional lymph nodes are not removed. Compared with those who have cervical cancer, the patients are older, more often poor surgical risks, and the pattern of lymph node involvement is less favorable. In certain cases, however, pelvic lymphadenectomy may contribute a feeling of greater postoperative security, especially when there is involvement of the

lower portion of the uterus and the patient is young and a good surgical risk. It was on this basis that H. W. Johnston,[2] of our clinic, published a description of his technique in 1942. This has been carried out successfully on a small number of patients who are included in this review, without any postoperative complications or unfortunate sequelae.

The planned method of treatment is applicable only to those cases which are considered operable. There remain the technically operable who, because of age or associated medical conditions, are poor surgical risks, and the inoperable whose disease has advanced beyond the hope of surgical cure. The latter groups are treated by intravaginal as well as intracavitary radium and high voltage therapy at 400 kv. delivered on 6 pelvic ports.

In order to obtain the best results with radium, certain basic factors must be considered:

1. A cancer-lethal dose should be delivered throughout the volume of tissue involved.

2. Necrosis of uninvolved tissue should be avoided.

It is well recognized that dosage stated in milligram hours gives only a vague indication of the tumor dose throughout the uterus. Accurate estimation is possible, however, using Paterson and Parker's[3] method or Edith Quimby's[4] tables.

Three forms of radium application are used, depending on the length and capacity of the uterine cavity. In a small uterus either two tandem pairs with a length of 4.5 cm., containing 60 mg. of radium are used, or three tandem pairs with a length of 6 cm., containing 60 mg. of radium. Table III shows that it is possible to deliver a cancer-lethal dose with either applicator at a depth of 2 cm., but the intensity is much more severe with the shorter applicator and, therefore, the risk of necrosis is greater.

TABLE III. COMPARATIVE DEPTH DOSE IN TWO INTRAUTERINE APPLICATORS

ACTIVE LENGTH 4.5 CM.		ACTIVE LENGTH 6 CM.	
DISTANCE FROM RADIUM	DOSAGE PER 3,720 MG. HR.	DISTANCE FROM RADIUM	DOSAGE PER 4,500 MG. HR.
2 cm.	6,000 r	2 cm.	6,000 r
1.5 cm.	9,300 r	1.5 cm.	8,800 r
1.0 cm.	16,500 r	1.0 cm.	14,500 r
0.5 cm.	41,000 r	0.5 cm.	33,000 r

In 1937, the late G. E. Richards adopted the principle of multiple applicators which had been advocated by Heyman.[5] The principal use of these was in the large uterine cavity, and the uterine cavity distorted by fibroids. These applicators consist of aluminum containers 3 cm. long, with an inside length of 2.4 cm., and a wall thickness of 1 mm. In these fit radium tubes 2.2 cm. in length with 1 mm. platinum filter. A stiff wire handle is attached, one end of which projects through the cervix and vagina so that the applicator may be guided into any desired position within the uterus. An arrangement of six at the fundus and four toward the cervix is satisfactory. Obviously, it is difficult to calculate the resultant dose as the

insertions are not constant and self-filtration of the radium occurs. Dosage meters to measure the dose as it is delivered are not in general use, but Lederman[6] has produced a probe type of direct reading dosage-rate meter which is an effective means of measuring the dose delivered by radium applied in this manner. An x-ray should be taken to determine the actual distribution of radium tubes with the applicators in position (Fig. 1).

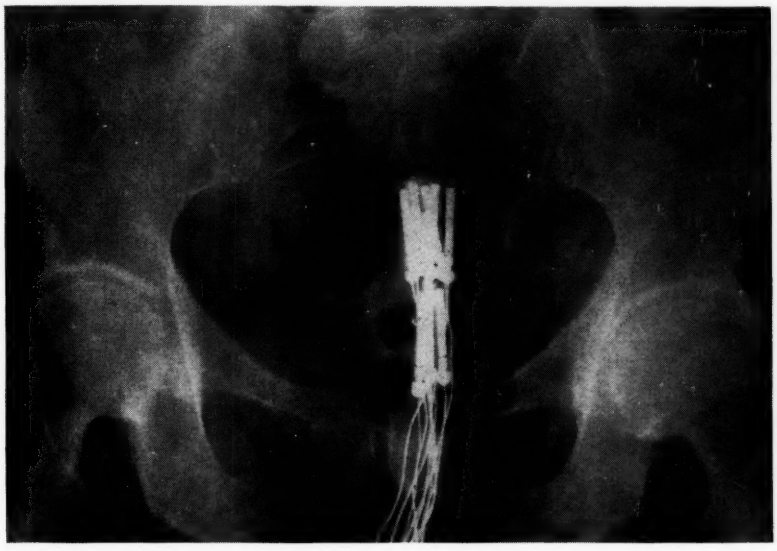

Fig. 1.—Radiogram showing multiple applicators in uterus. The distribution is six at the fundus and four at the lower uterine segment.

The pattern of isodose curves can be plotted about the applicators. Less surface intensity is delivered with a depth dose equal to either of the single applicators and an appreciably greater dose is delivered to the cornual areas (Fig. 2).

It requires 6,750 mg. hr. to deliver 6,000 r 2 cm. away from the edge of the radium which in this case is 2.75 cm. from the center of the uterus. The volume of tissue so radiated is sufficient to cover all but the largest carcinomatous mass.

It has been our experience that preoperative radium therapy is followed by an appreciable decrease in the size of the enlarged uterus and by a cessation of bleeding and discharge. The tumor area is markedly affected, and sometimes the tumor has apparently disappeared completely. Frequently, however, the dominant feature of the irradiated uterus is necrosis, as sufficient time has not elapsed for surface healing to have occurred.

When radiotherapy is the only means of treatment, two applications of radium are made within a month instead of one massive dose. By this means it is possible to take advantage of the decrease in the size of the uterus and of the tumor which follows the primary application.

Table IV presents the five-year survival rate, which for all patients seen has been 46.2 per cent. It cannot be considered a basis for comparison of

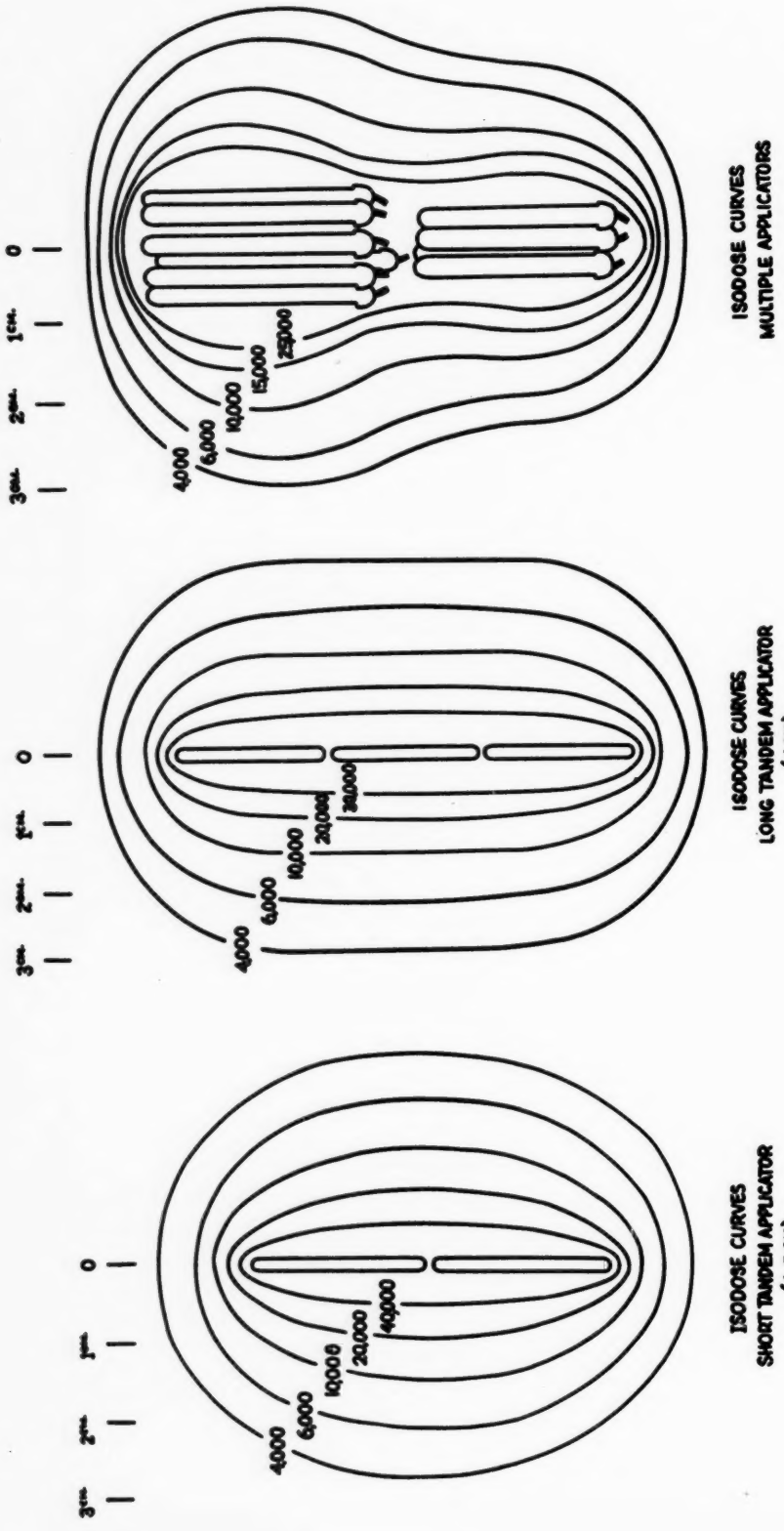

Fig. 2.—Comparative isodose curves of the three types of intrauterine radium applicators.

methods of treatment as the patients comprising the various groups have differed materially. Two factors have contributed to lowering the survival rate. The follow-up liaison between the surgical wards and the cancer follow-up clinic was unsatisfactory in the early years, and the proportion of very advanced lesions was unduly high, as many were referred for consideration of radiotherapy by outside surgeons when all hope of successful surgery was past. An analysis of the patients treated surgically at the Toronto General Hospital is presented in Table V. Attention is drawn to the fact that when a net rate is applied the survival rate for planned therapy becomes 84.6 per cent, and the rate for all surgically treated cases 72.9 per cent. The two supravaginal hysterectomies were incomplete operations because of extensive tumor and technical difficulty.

TABLE IV. FIVE-YEAR SURVIVAL*
1937-1947

METHOD OF TREATMENT	NO. OF CASES	A. & W.	D. D.	D. E. D.	UNTR.	% SURVIVAL
T. G. H. Surgery	68	43	16	2	7	63.2
T. G. H. Radiation only	100†	30	64	3	3	30.0
T. G. H. Not treated	7	0	7	0	0	0
Outside surgery	59	35	21	1	2	59.3
Total	234	108	108	6	12	46.2

*In statistical tables the following abbreviations are used:
A. & W.—alive and well.
D.D.—died of disease.
D.E.D.—died of extraneous disease.
Untr.—untraced.
†Includes 34 inoperable cases with only three 5-year survivals.

TABLE V. FIVE-YEAR SURVIVAL, SURGICALLY TREATED CASES, TORONTO GENERAL HOSPITAL
1937-1947

METHOD OF TREATMENT	NO. OF CASES	A. & W.	D. D.	D. E. D.	UNTR.	% SURVIVAL
Preoperative radiation and total hysterectomy	47	33	6	2	6	70.2
Total hysterectomy and post-operative radiation	15	8	6	0	1	53.3
Total hysterectomy only	4	2	2	0	0	50.0
Supravaginal hysterectomy	2	0	2	0	0	0.0
Total	68	43	16	2	7	63.2
		(Net survival rate)				
		All patients				72.9%
		Preoperative radium + hysterectomy				84.6%

As an example of the way in which circumstances alter cases, it is to be noted that of the fifty-nine patients referred by outside surgeons for post-operative radiotherapy, twenty-seven had been treated by subtotal hysterectomy, and the survival rate for them was 55 per cent, as compared with 62 per cent for the patients who had total hysterectomy. A probable explanation of this almost paradoxical result is that subtotal operations were undertaken without knowledge that a malignant condition was present and fortunately in many cases a very early lesion existed (Table VI).

TABLE VI. FIVE-YEAR SURVIVAL, OUTSIDE SURGERY
1937-1947

METHOD OF TREATMENT	NO. OF CASES	A. & W.	D. D.	D. E. D.	UNTR.	% SURVIVAL
Total hysterectomy and post-operative radiation	32	20	10	0	2	62.5
Supravaginal hysterectomy and postoperative radiation	27	15	11	1	0	55.5
Total	59	35	21	1	2	59.3

There have been three gradual changes in the treatment of the patients in the sixteen years under review. The first is that with better medical supervision and improved anesthesia a smaller number of patients have been considered only technically operable, so that, whereas up to 1947 one hundred patients were treated by radiotherapy to sixty-eight who were operated upon at the Toronto General Hospital, in the last five years this condition has been reversed and forty-eight have been treated by radiotherapy and seventy-six have been operated upon. Second, the dosage of intrauterine radium has been standardized and brought to an adequate level. This has had an appreciable effect on the results. Third, the planned method of treatment has been applied to an increasing proportion of the surgically treated patients, so that while it was used in forty-seven of sixty-eight cases operated upon up to 1947, in the last five years sixty-one of seventy-six have been so treated.

TABLE VII. THREE-YEAR SURVIVAL
1937-1947

METHOD OF TREATMENT	NO. OF CASES	A. & W.	D. D.	D. E. D.	UNTR.	% SURVIVAL
T. G. H. Surgery	68	51	10	0	7	75.0
T. G. H. Radiation only	100	44	52	2	2	44.0
T. G. H. Not treated	7	0	7	0	0	0.0
Outside surgery	59	37	20	0	2	62.7
Total	234	132	89	2	11	56.4

TABLE VIII. THREE-YEAR SURVIVAL
1948-1949

METHOD OF TREATMENT	NO. OF CASES	A. & W.	D. D.	D. E. D.	UNTR.	% SURVIVAL
T. G. H. Surgery	44	37	7*	0	0	84.0
T. G. H. Radiation only	15	5	8	0	2	33.3
T. G. H. Not treated	0	0	0	0	0	0.0
Outside surgery	20	14	4	0	2	70.0
Total	79	56	19	0	4	70.9

*Including 2 operative deaths.

Also, in recent years the surgeons who refer their patients to this Institute for auxiliary treatment have shown a gradually increasing appreciation of the value of preoperative radium therapy. Tables VII and VIII show the effect of these changes in methods of therapy. Table VII shows the three-year survival rate up to 1947, and Table VIII shows the three-year survival rate for 1948 and 1949, inclusive. The rate has risen from 56.4 to 70.9 per

cent. The factors which are responsible for the improvement are an increased use of surgery, and the rise in the surgical salvage rate due to a greater use of planned therapy. The wider application of surgery to patients previously considered only technically operable shows its effect in a fall in the salvage rate of patients treated by radiotherapy as these patients are now more predominantly inoperable. Two operative deaths have resulted from this wider application of surgery to patients who were not good operative risks.

Pathology

The assessment of the effectiveness of intrauterine radium as an adjunct to the surgical treatment of corpus cancer, or as a means of treatment in itself, carried with it the necessity of reviewing the material on which the diagnosis had originally rested. Furthermore, in order to implement a uniformity of histological criteria it seemed most desirable that the review be undertaken by a single individual. This must not be construed as a lack of faith either in the diagnostic ability of colleagues, or in the clinical acumen of the attendant physician, but is merely an acknowledgment of the several interpretations commonly given to a group of endometrial changes about which it is frequently difficult, if not impossible, to be dogmatic. Differences in interpretation, when given by competent individuals, lie properly outside the realm of diagnostic error.

Of the 421 cases referred to, the relative material was available on 386. These formed the basis for the purely pathological considerations which follow. Of these 386 cases, the diagnosis of endometrial carcinoma was questioned in twenty-eight.

TABLE IX. COMPARATIVE SURVIVAL RATES AFTER PATHOLOGICAL REVIEW
1937-1949

GROUP	TOTAL CASES	THREE-YEAR SURVIVAL	PERCENTAGE	
			GROSS	NET*
All cases	253	151	59.6	67.1
Confirmed cases	229	135	58.9	64.9
Borderline cases	24	19	79.1	100

*Excluding patients who died of extraneous disease and those untraced.

The term "borderline" has been used in Table IX to indicate those cases in which the endometrial changes were thought more probably representative of atypical hyperplasias than carcinoma. The survival rate for this group, when compared with that for the unequivocal cases, tends to support this probability.

Based on the description by Cullen[7] and, later, Schröder,[8] the term "endometrial hyperplasia" has, through popular acceptance, come to have a limited meaning. It has reference to the marked disparity of size and irregularity of outline of the endometrial glands, and the obvious activity of both stroma and epithelial elements. It is a condition encountered predominantly during reproductive life, and doubtless reflects an atypical reactivity of the endometrium to hormonal stimulation. A causal relationship to carcinoma has yet to be finally demonstrated.

Qualification of this term, namely, atypical glandular hyperplasia, refers to changes similar to those previously described, and having, in varying degrees, the added features of stratification, metaplasia, and, frequently, a noteworthy failure of the endometrial stroma to participate in the hyperplasia to the same degree as do the glandular elements.

It is, for obvious reasons, desirable that, where possible, these changes be identified and recognized by such characteristics as they possess.

The ionizing effect of therapeutic radiation on living cells which is, of course, not selective in its action, frequently induces changes of such a bizarre nature that the positive identification of residual tumor following radiation becomes a matter of extreme difficulty. Its effects represent, among others, the delayed result of altered cell-membrane permeability, and chromosomal cohesion. Major degrees of cell atypism are, therefore, no longer an exclusive hallmark of malignancy (Figs. 7 and 8).

Frequently used by the radiotherapist as an indication for further therapy, the positive identification of residual tumor in an irradiated site now becomes a matter of great technical difficulty, and frequently demands an even more rigid implementation of criteria than was necessary in order to make the original diagnosis. It requires, furthermore, a certain familiarity with the cellular changes encountered in previously irradiated tissues.

Since we have presented evidence which indicates the effectiveness of preoperative irradiation in influencing the prognosis, a painstaking evaluation of the irradiated lesion is more than ever incumbent on the pathologist charged with this responsibility.

TABLE X. EFFECT OF RESIDUAL CARCINOMA ON THE SURVIVAL RATE*
1937-1949

GROUP	TOTAL CASES	THREE-YEAR SURVIVAL	PERCENTAGE	
			GROSS	NET†
Confirmed residual	65	31	47.7	50.0
Queried residual	17	14	82.1	93.3
No residual	20	16	80.0	100.0

*After pathological review.
†Excluding patients who died of extraneous disease and those untraced.

The phrase "queried residual" in Table X refers to a group of cases which, on critical review of the material available, were thought to exhibit merely radiation changes in endometrial epithelium. This group had previously been considered as residual carcinoma.

As with the assessment of the cases of endometrial hyperplasia, the pathological reviews were undertaken without knowledge of the clinical course, and the two aspects were integrated only after a final pathological opinion had been reached.

It is perhaps reasonable to suggest that the detection of invasive carcinoma in an adequately radiated uterus depends, in great part, upon the thoroughness with which the search is undertaken. We are far from satisfied

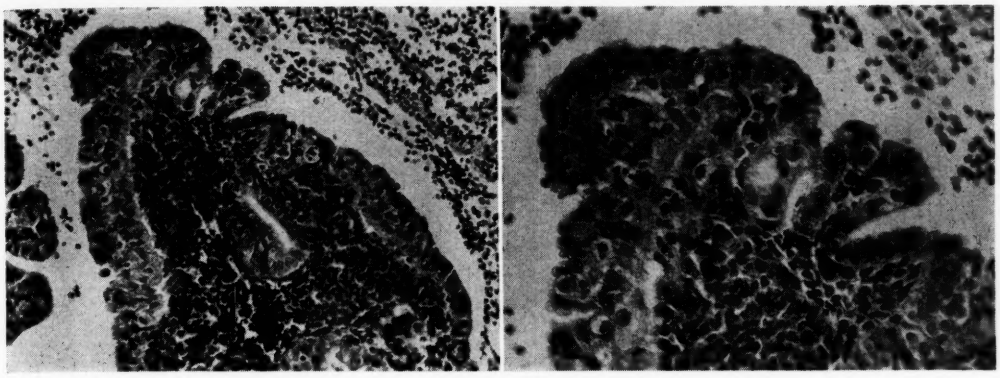

Fig. 3. Fig. 4.

Fig. 3.—Atypical hyperplasia of endometrial epithelium. (×154, reduced ⅓.)

Fig. 4.—As in Fig. 3, showing transition from columnar epithelium to area of metaplasia. (×308, reduced ⅓.)

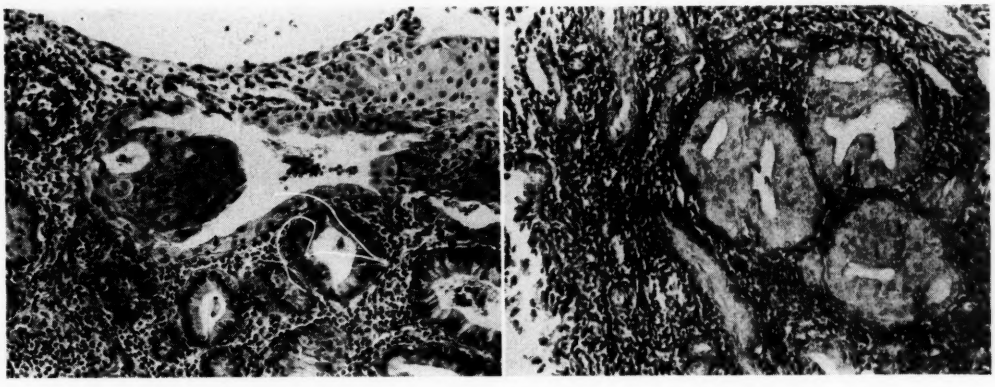

Fig. 5. Fig. 6.

Fig. 5.—Projection of mass of squamous epithelium into lumen of distended endometrial gland—squamous metaplasia. (×115, reduced ⅓.)

Fig. 6.—The lumina of endometrial glands narrowed by atypical hyperplasia of lining elements. (×115, reduced ⅓.)

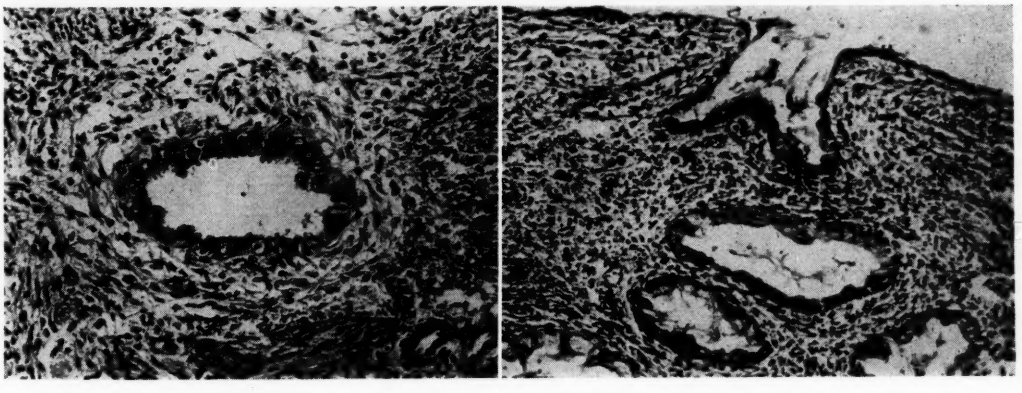

Fig. 7. Fig. 8.

Fig. 7.—Radiation effect on normal endometrial epithelium. Note altered staining reaction of nuclei and the presence of vacuoles. (×154, reduced ⅓.)

Fig. 8.—Same as Fig. 7. (×144, reduced ⅓.)

that an adequate or thorough search was made in much of the material examined, material which is, unfortunately, no longer available for rechecking. However, utilizing such evidence as could be obtained, an attempted correlation has been made between the presence of invasive tumor, and the survival rate in those instances in which hysterectomy formed a part of the treatment (Table XI).

TABLE XI. EFFECT OF MYOMETRIAL INVASION ON THE SURVIVAL RATE 1937-1949

GROUP	TOTAL CASES	THREE-YEAR SURVIVAL	PERCENTAGE	
			GROSS	NET*
With invasion	91	57	62.6	65.5
Without invasion	54	44	81.5	91.6

*Excluding patients who died of extraneous disease and those untraced.

Conclusions

1. The 421 cases which provide the material for this review represent a broad clinical group including, as they do, a considerable number of cases for which radiotherapy presented the only possible hope of cure.

2. In the group of patients which has been presented, 7 per cent were of doubtful malignancy. The effect of this on the survival rate must be recognized.

3. The presence of residual (postradiation) carcinoma and myometrial invasion influence the prognosis.

4. In the 16 years under review there has been an increasing use of preoperative radium with an evident improvement in the results of treatment.

5. In our experience the planned method of therapy appears to give the best results.

References

1. Heyman, James: Acta radiol. **8**: 363, 1927.
2. Johnston, H. W.: Surg., Gynec. & Obst. **74**: 1003, 1942.
3. Paterson, R., and Parker, H. M.: Brit. J. Radiol. **11**: 252, 1938.
4. Quimby, Edith: Radiology **43**: 572, 1944.
5. Heyman, James: Acta radiol. **7**: 363, 1927.
6. Lederman, M.: Brit. J. Radiol. **23**: 430, 1950.
7. Cullen, T. S.: Cancer of the Uterus, Philadelphia, 1900, W. B. Saunders Company.
8. Schröder, R.: Arch. f. Gynäk. **104**: 27, 1915.

Discussion

DR. HAROLD S. MORGAN, Lincoln, Neb.—A survey of the recent literature dealing with carcinoma of the body of the uterus indicates that planned programs for the treatment of this neoplasm are producing excellent results. Dr. Cosbie and his associates have shown substantial improvement in the survival rate in their clinics since adopting their planned method of treatment. Confining myself to that part of their presentation that is within my experience, I will comment on the problems of fundal malignancy as we in a midwestern rural area see it today.

A recent study conducted by Gorthey and Tweeddale of our institution revealed the fact that the incidence of fundal malignancy was greater than the incidence of cervical malignancy. A total of 28, 530 routine surgical specimens in the files of the Department of Pathology in our hospital, collected from patients in the hospital and from southeastern

Nebraska over a period of 13 years, were reviewed. One hundred forty-four cases of corpus malignancy were found as compared to 95 cases of cervical malignancy. Ninety-three per cent of the fundal malignancies were adenocarcinoma of the uterus. The statewide significance of this trend is well discussed in their paper which is to be published soon. In a recheck of the records of those patients treated in our hospital we find confirmation of Dr. Cosbie's and others' statements that there is a high incidence of hypertension, obesity, and diabetes noted as complications in these patients. The average age of Nebraska women who develop carcinoma of the fundus is 66.7 years, whereas Dr. Cosbie reports the average age of his group as being 59.2 years. Inasmuch as Nebraska seems to lead the nation in terms of longevity, the average length of female life in Nebraska being 70 years, it is reasonable to assume that, since fundal malignancy is a disease of later life, as our over-all life expectancy is increased we shall witness a definite ascendency of the fundal rate over the cervical rate throughout the nation. Brewer has likewise noted and commented on this change of ratio. If this trend persists, then the results reported by Cosbie, Scheffey, Miller, Lampe, Randall and Stearns, among others, who advocate a combined or planned treatment program, will be doubly important, bearing as they do a promise of a higher percentage of cures.

At the Lincoln General Hospital we are presently treating carcinoma of the endometrium by a combined program utilizing both x-ray and radium followed by surgery. This method somewhat parallels that reported by Lampe of the University of Michigan, save that wherein the Michigan group utilizes the deep x-ray therapy and surgery plan of attack on most of their patients, reserving the x-ray-radium-surgery sequence for those patients considered technically operable, we have preferred, in most cases since 1946, to utilize radium, 6,000 to 7,000 mg. hr. and x-ray 2,000 r in air to each of 4 pelvic ports, followed in six to eight weeks by total hysterectomy and bilateral salpingo-oophorectomy. No lymph gland resections have been done. Our small series of 81 patients with adenocarcinoma of the endometrium collected during the past ten years may be broken down as shown in Table I.

TABLE I. TYPES OF THERAPY IN 81 CASES OF CARCINOMA OF THE ENDOMETRIUM

TOTAL CASES	COMBINED X-RAY, RADIUM, AND SURGERY	SURGERY ONLY	X-RAY AND RADIUM ONLY	DILATATION AND CURETTAGE ONLY, OR TERMINAL CARE
81	31	21	25	4

Noting Dr. Cosbie's three-year survival rate of 80 per cent in those cases which present no residual cancer as contrasted to a 47.7 rate for those which show residual malignant cells, we are encouraged and, although we have as yet no data on our survival rate, it is interesting to note the result of our planned therapy as it relates to residual malignant cells (Table II).

TABLE II. INCIDENCE OF SURVIVING MALIGNANT CELLS AFTER RADIATION

TOTAL CASES, IRRADIATION AND SURGERY	RESIDUAL MALIGNANCY	NO RESIDUAL MALIGNANCY
31	11	20

During the past thirty days our attention has been directed to three patients who had developed adenocarcinoma of the endometrium 8, 7, and 5 years after having had a curettage and receiving radium therapy for menopausal bleeding. A further search of our records has produced two additional cases, making a total of 5 in all, or roughly 6 per cent. We are not prepared to say that radiation therapy is carcinogenic, but rather

from our experience that radium used to control endometrial hyperplasia does not prevent cancer from developing in later years. I would appreciate Dr. Cosbie's opinion relative to this problem.

DR. CLYDE L. RANDALL, Buffalo, N. Y.—I was glad to see Dr. Cosbie's evaluation of treatment on the basis of the patient's condition at the end of three or five years. Most evident in discussions of the in-situ stages of malignant disease, there seems to be an increasing tendency to attribute considerable significance to the histologic findings in the tissues removed. We all know, however, that an evaluation of treatment also requires time, for it seems unlikely that, under "routine" or usual circumstances, removed tissues will be examined with enough thoroughness to justify confidence in a prognosis based upon the presence or absence of demonstrable metastasis.

I assume that most of us in this audience are no longer trying to decide whether we should employ irradiation *or* surgery in the treatment of adenocarcinoma. Heyman's eighth annual report indicates that both "primarily surgical" and "primarily irradiative" treatment is accomplishing the same five-year results, and, among gynecologists, a combination of irradiation *and* surgery seems to be preferred. Even so, we still may not know how much irradiation is optimal, how it should best be applied before hysterectomy, nor how extensive an operation should ultimately be done.

Although multiple-tube techniques give a more effective distribution of irradiation throughout the uterus, and Dr. Cosbie has added another report indicating better results with such improved methods, I believe it a mistake to judge the effectiveness of our treatment on our ability to eliminate all recognizable cancer *in the tissues we are going to remove*. Since hysterectomy is to follow soon after the application of radium, I wonder if we should not make a greater effort to deliver a tumoricidal dose to the paravesical and pararectal tissues that are not to be removed, rather than concentrating upon the uterus itself. With this in mind, during the past year we have started a series of patients that, so far as radiation is concerned, are to be treated exactly as if they had squamous-cell carcinoma—with dosage distributed in the vaginal fornices rather than concentrated entirely within the cavity and canal. Granting, however, that the chief problem is not that of local recurrence after present methods of treatment, in all probability more irradiation along the lines of lymphatic spread would not eliminate distant metastasis any more effectively than does surgical excision of those routes.

Several years ago, we became interested in the possibility that we could lower the mortality due to endometrial carcinoma by a more extensive operation. Since 1947, in 35 cases of adenocarcinoma, a radical type hysterectomy has been done, mobilizing two-thirds of the anterior vaginal wall plus a wide dissection of parametrium from below and removal of all nodes along iliac, hypogastric, and obturator vessels with the uterus and adnexa from above. Eight weeks to a year prior to surgery, each patient had received a single intrauterine application of 6,000 to 6,500 mg. hr. of radium, applied in approximately 120 hours by means of a single applicator anchored in the axis of the cervical canal. In 41 per cent of the cases operated upon, viable-looking carcinoma was found in the removed uterus. Six cases should be excluded because they were primarily of endocervical origin. Of the twenty-nine remaining cases, positive nodes were found in only three. Two of the three with positive nodes also had metastatic tumor in the adnexa and, in two other cases with negative nodes, extension into an ovary was recognized in one case and there was extension into a tube in another. Thus metastasis was evident in six of the twenty-nine cases, whereas all growth may have been removed in twenty-three of the twenty-nine, or 79 per cent of the cases so treated.

Only twelve of this group were operated on prior to August, 1948, and are now available for evaluation of five-year results. One has been lost, and must be considered dead of disease. Two are known dead, one of recurrent disease and one of causes unrelated to the adenocarcinoma. Six and one-half years after operation, one patient recently developed an acute intracranial lesion which was considered inoperable. Autopsy revealed that death was due to a rapidly growing glioma. No evidence of adenocarcinoma

was found. The one known dead of disease to date, after five years with no evidence of local recurrence, developed carcinomatosis of the lungs. At autopsy six years after radical hysterectomy and pelvic node dissection no evidence of adenocarcinoma was found in the pelvis or abdomen, but the histologic picture in the lung was similar to the adenocarcinoma previously in the uterus.

Among nine of the twelve alive with no evidence of disease more than five years after operation, hypogastric nodes were positive in one of the three in whom cancer was found in the uterus after the hysterectomy and in a fourth, among the nine survivors, metastasis was evident in one ovary.

Our limited experience to date suggests that if surgery more radical than the usual "panhysterectomy" is to be employed, we should take Henriksen's data into consideration and remove the inguinal as well as the obturator, hypogastric, and iliac nodes, recognizing, however, the possibility of aortic node involvement and an eventually fatal spread in spite of a most adequate dissection of the pelvis.

Adenocarcinoma of the uterus *is* an important subject, where progress is being made, but there is still need for improvement.

DR. WILLIAM ANDERSON, Toronto, Ont.—As a surgical pathologist, concerned largely but by no means exclusively with the problems of my gynecological clinical colleagues, I would venture to suggest to this audience that the problems which they face are in no way different from the problems facing the thyroid surgeon, if I may coin the term, or the surgeon concerned with the treatment of the so-called malignant polyp of the gastrointestinal tract, around which I assure you, considerable furor exists. While many tissues evidence altered reactivity to insult—be it hormonal, infective, or of an unknown type—these changes must be recognized and differentiated, where possible, from cancer, which is, after all, a prognostic term. That such highly reactive tissues may eventually, and more frequently perhaps, be the site of malignancy is possible, and perhaps probable. This suspicion must not, for very obvious reasons, be allowed to influence or readily to change the criteria of malignancy that are old, well tried, and certain.

Finally, bizarre changes are commonly encountered in tissues which have been heavily irradiated; these changes are, we believe, entirely the result of irradiation.

DR. COSBIE (Closing).—It is certain that in the treatment of malignant tumors the best results are obtained by the cooperation of gynecologist and radiotherapist. To these we might well add the pathologist and also the radiophysicist. Without the help of the latter an accurate appreciation of radiation dosage is impossible.

The chief criticism of the use of preoperative high voltage therapy is that it is very time consuming. A cancer-lethal dose of radiation can be given to the tumor area much more rapidly and more efficiently by the use of radium.

In the group of patients who provided the material for our paper a considerable number received postoperative roentgen therapy. It was given to all those who were referred after surgical treatment elsewhere except a small number recently who have been referred for preoperative radium treatment. It was given to some patients who were operated upon in the Toronto General Hospital and who had not had the benefit of preoperative radium therapy. It was also given to those patients who were treated by the planned method of therapy and who had an extension of the tumor beyond the body of the uterus. It must be borne in mind, however, when we use postoperative therapy to do what we have failed to accomplish by operation, that the lymph nodes are frequently involved above the brim of the pelvis and distant metastases may have already developed. On the same basis one questions the advisability of subjecting this older group of patients to routine pelvic lymphadenectomy. It has been proved over and over again that when distant metastases are present they are very hard to recognize, and it may be that the removal of the lymph nodes has more prognostic significance than therapeutic value.

Original Communications

OXYTOCIN AND MILK EJECTION

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THE oxytocic, pressor, and antidiuretic activities of extracts of the posterior pituitary gland are well known and are widely used in practice. Less well known, except to students of the physiology of lactation (see reviews by Petersen,[11] 1944; Folley,[3] 1947; and Newton and Newton,[7] 1948) is the fact that posterior pituitary gland extracts stimulate, some few seconds after intravenous injection, the expression of milk from the mammary gland of a lactating animal. This expression of milk is now called the "letting-down" or "ejection" of milk and is part of the milk "let-down" or "ejection" reflex in animals. This same reflex has been called by Waller the "draught" reflex in the lactating woman. This reflex is now thought to be essentially the same in all mammals (Whittlestone, Bassett, and Turner,[23] 1952).

Normally, the reflex is initiated by the suckling or nuzzling of the nipples or the breast of the mother by the young. This action carries afferent stimuli by nerve pathways to the brain. So stimulated, the neurohypophysis liberates the hormone which then becomes the humoral efferent stimulus to the mammary gland. The mode of action of the hormone in the mammary gland is not known definitively. However, that the action of the hormone is directly on the gland is reasonably well established. The reflex may be initiated by sounds or actions which are associated with milking or nursing, such as the banging of milk pails in the dairy barn or the cry of the child. The reflex may be inhibited by fright or any disturbing stress. It has been inhibited in cows by injecting epinephrine.

Since none of the texts in English on obstetrics and gynecology or pediatrics which have come to our attention and are currently in use discuss the milk-ejection activity of the posterior pituitary gland, it seems desirable to review briefly the pertinent literature before presenting our results on the milk-ejection activity of purified oxytocin.

History

The milk-ejection activity of the posterior pituitary gland extracts was first described by Ott and Scott[10] in 1910. They administered crude extracts intravenously to a lactating goat and measured the increased flow of milk

ensuing some few seconds after the injection. Their observations were confirmed almost immediately by Schäfer and MacKenzie[15] on the cat and dog. MacKenzie,[6] in 1911, described this work in detail and recorded the administration, once, of a commercial extract to a lactating woman 10 months post partum who was admitted to the hospital for the treatment of a breast abscess. The results were equivocal. In these first reports the view was taken that the posterior pituitary extracts stimulated the secretion of milk.

In 1913, Schäfer[14] described the work of Sumpter who administered posterior pituitatry extract intramuscularly on four occasions to a 28-year-old lactating multiparous woman 5 months post partum who was having difficulty satisfying the needs of her second child at the breast. Though milk ejection occurred, the conclusion arrived at in this one case agreed with that arrived at by Gavin[4] this same year, who established with cows that this activity of the posterior pituitary extracts stimulates the outflow of milk already in the gland, but does not, over a period of time, increase the total yield of milk.

During the next eighteen years several papers appeared in the literature confirming these early observations. But the belief seemed to persist that the posterior pituitary extracts were galactagogic in nature. In 1930 Turner and Slaughter[17] reaffirmed the earlier belief that the milk-expressing activity of Pituitrin in the cow was on some "mechanism normally effective during the milking process" and that it was not a galactagogic activity. Subsequently Ely and Petersen[2] (1941) observed milk-ejecting activities in the cow of commercial preparations of both oxytocin and vasopressin, the latter being the least active. They considered the milk "let-down" activity of the commercial extract of vasopressin to be due to contamination with oxytocin. Similar results were obtained by Turner and Cooper[16] (1941) in lactating rabbits. However, these authors suggested the possibility of a separate milk "let-down" hormone, on the basis of the fact that the milk "let-down" activity of the commercial extracts of vasopressin was greater than the amount of oxytocin present.

By using purified oxytocin prepared by Livermore and du Vigneaud[5] (1949) and highly purified vasopressin prepared by Turner, Pierce, and du Vigneaud[18] (1951), which contained less than 5 per cent oxytocin as judged by its leucine, isoleucine content, Whittlestone[22] (1952) has been able to show, using the lactating sow as a test animal, that purified oxytocin has milk-ejection activity equivalent to its oxytocic activity while highly purified vasopressin had an activity equivalent to one-fifth its pressor activity. Cross and Van Dyke[1] (1953) using oxytocin prepared by Pierce, Gordon, and du Vigneaud[12] (1952) and a highly purified vasopressin free of oxytocin prepared by Popenoe, Lawler, and du Vigneaud[13] (1952) obtained essentially similar results with the lactating rabbit. Thus, it appears most probable that oxytocin is the principal milk-ejection hormone of the posterior pituitary, though vasopressin also has inherent milk-ejection activity.

Waller,[21] in 1943, in a study of lactation in women, concluded that the milk "let-down" reflex in the human being is the same as in animals. The sensations felt when the reflex is initiated may be described variously by the patients. In Waller's study "a feeling like pins and needles" or a "drawing" were most frequently used. Since this sensation plus the hardening of the

breasts accompanying it has been called by women the "draught," Waller has called the reflex the "draught" reflex. In 1948 Newton and Newton[7] extended the observation on the "draught" or "let-down" reflex in the human being. Using one patient 7 months post partum they demonstrated that Pitocin given intramuscularly would cause the "let-down" of milk. They demonstrated further in this one patient, as had been shown previously in cows, that distractions and other emotional disturbances tended to inhibit the "let-down" of milk.

In 1950, Newton and Newton[8] correlated in 103 cases the ability of patients to breast feed with the completeness of the emptying of the breast after feeding. The degree of emptying was estimated by determining the amount of milk obtained by the baby. Then the amount which could subsequently be obtained by breast pump and by breast pump after Pitocin. The ratio of the amount of milk obtained after Pitocin to the total milk obtained by baby and breast pump expressed as a percentage was called the Pitocin percentage and was used as an index of the completeness of the emptying of the breasts. In general, those successful at breast feeding had lower Pitocin percentages because they "held up" less milk. In 1951, Newton and Newton[9] showed that Pitocin could be used to reduce breast engorgement.

All the previous studies of the activity of oxytocin in the human being have been carried out with preparations of oxytocin which varied from simple extracts of the posterior gland to purified preparations, which, though better than simple extracts, still contained considerable inert material and small but still measurable amounts of pressor and antidiuretic activity. Now that oxytocin has been prepared free of these activities and is available in sufficient quantity for clinical trial it becomes possible to determine the effectiveness in the human being of oxytocin uncontaminated by any of the other associated physiological activities of the posterior pituitary (i.e., pressor and antidiuretic activity).

Further, chemical studies of the structure of oxytocin, all reported elsewhere,[20] have shown that oxytocin is a polypeptide (actually, an octapeptide amide) composed of eight amino acids. Knowledge of the structure has made it possible to synthesize from eight naturally occurring amino acids and ammonia, an octapeptide amide which, in so far as could be ascertained, represents oxytocin.[19] The milk-ejection activities of both preparations are described. (The preparation isolated from natural sources is called oxytocin. The preparation which has been synthesized is designated as oxytocin-S.)

In so far as we have been able to determine, no previous studies have been reported as to the appropriate dose of oxytocin required to elicit the milk-ejection response in the normal lactating woman in the early puerperium. Newton and Newton used 3 units of Pitocin intramuscularly and subcutaneously. On the basis of work done in animals this dose level might be larger than is actually required. Therefore, we have determined the response obtained when pure oxytocin is given at various dose levels intravenously and intramuscularly to lactating women in the early puerperium. This has been done as a necessary orientation study preliminary to the further evaluation of the pure oxytocin as a therapeutic agent.

Materials and Method

Several different procedures might have been applied to test the milk-ejection activity of oxytocin in the human being. For our immediate purpose a qualitative test was deemed sufficient. Since milk secretion is not generally established until the third to fourth postpartum day, the fourth postpartum day was selected as the earliest day on which a response might reasonably be expected consistently. Generally mothers were selected who appeared clinically to have milk except in the few instances recorded below. All mothers were inpatients at this Hospital and had had essentially normal pregnancies, labors, and postpartum courses.

The test procedure is carried out as follows. Shortly before the mother is to nurse her baby the hormone is injected. A positive response to the hormone is considered to be obtained when an outflow of milk can be observed shortly after the injection. The time elapsed from the completion of the injection to the appearance of milk is recorded. Some patients who did not respond to the injection with an actual flow of milk did report subjective symptoms such as a tingling sensation in the breasts. Such reports, either voluntary or elicited, were not considered a positive response.

TABLE I. RESPONSES OF LACTATING WOMEN IN THE EARLY PUERPERIUM TO OXYTOCIN

GROUP	HORMONE	ADMINISTERED	DOSE	PATIENTS	DAYS POST PARTUM	POSITIVE RESPONSES	TIME TO RESPONSE	
							AVERAGE	RANGE
			Units	No.		No.	Sec.	Sec.
1.	Oxytocin	I.V.	1*	8	4-7	6	24	20-32
2.†	Oxytocin 1st	I.V.	0.25	6‡	5-7	3	22	20-25
	Oxytocin 2nd	I.V.	0.25-1.0	4	5-6	4	37	15-60
3.	Oxytocin	I.M.	3*	12	4-5	12	54	45-60
4.	Oxytocin-S	I.V.	0.5	12§	4	9	32	25-45
5.	Oxytocin-S	I.V.	0.5	4	5	4	24	20-35
6.	Oxytocin-S	I.V.	0.1-1.0	5	6-8	5	27	15-30
7.	Oxytocin	I.M.	2*	6	4-5	6	50	45-60
8.	Oxytocin	I.M.	1*	8	4-5	6	48	40-55

*Solution contained 10 units per cubic centimeter. All others 1 unit per cubic centimeter.
†Explained in detail in text.
‡The three who did not respond were given a total of 1 unit of oxytocin.
§Two were adjudged clinically before the injection was made to have no milk.

Results

The first group of patients to be injected (Group 1 in Table I) received about 1 unit of oxytocin intravenously. This is many times the dose level which would be estimated as being required from the previous work on cows. However, it was about the smallest volume of solution which could be injected using ampules containing 10 units of oxytocin per cubic centimeter. There were 8 patients in the group 4 to 7 days post partum. Two failed to give a positive response (one 4 and the other 6 days post partum). The small volume injected might have led to the failures, so ampules containing 2+ c.c. of solution with oxytocin at a concentration of 1 unit per cubic centimeter were prepared for us by our pharmacy. The actual weight of oxytocin in these solutions is ex-

tremely small. Oxytocin has an activity of about 500 units per milligram. Thus a solution which contains 1 unit per cubic centimeter contains 2 micrograms or 0.000002 gram per cubic centimeter.

Since the milk-ejection reflex can be initiated as a conditioned reflex, and we had chosen the time for testing to be before a scheduled nursing period, and since the concentration of active material in the dilute solution is extremely small, it became imperative to determine whether oxytocin was responsible for the ejection of milk or whether injection of water might not elicit this same response before a nursing period. To put this to test, one of us (K. N.) was given pairs of specially prepared ampules as unknowns. One of these ampules might or might not contain oxytocin. If it did contain oxytocin, it was at a concentration of 1 unit per cubic centimeter. (This was known to K. N.) The ampules were labeled with a number and a letter, "A" or "B." The contents of "A" was administered first. If a response was obtained, "B" was not given. If no response was obtained, "B" was administered. The patient was told only that she was going to receive an injection. She was not told what to expect.

With the use of this procedure, oxytocin was administered intravenously first 6 times with a positive response in 3 and no response in 3. One of these was an elderly primigravida, probably without milk. The 3 who did not respond to oxytocin *did not* respond to the subsequent injection of water. Water was given first in 5 cases. None of these responded to the injection of water. In 4 of these, oxytocin was given in the second injection with a positive response in all the patients. In the fifth case, there was water in the second ampule, too, and the patient failed to respond to this second injection. The time of response of these patients is recorded in the table as Group 2.

These results do show that no response is obtained to the injection of water. We should have liked to have had a better response by those who received the oxytocin first. A repetition of this experiment now might accomplish this for two reasons. Increased experience has made it possible to judge clinically those who probably have or do not have milk. This contention is supported by some data in Group 4 with oxytocin-S. Second, in retrospect, it is possible that these ampules contained very little oxytocin. Reassay of a surplus ampule showed very little oxytocic activity. We now view the negative results of this series the most important aspect, i.e., that no patient responded with a flow of milk after the injection of water.

The optimum and minimum doses have yet to be established. The lowest dose tried has been 0.1 unit to which the usual response was obtained (1 patient, sixth postpartum day, Group 6). Several have responded after only 0.25 unit. Though the minimum dose has not been established, 0.5 unit seems to be approximately an optimum dose since a positive response was consistently obtained at this level with oxytocin-S (Groups 4, 5, and 6). Out of 19 patients who were expected to give a positive response at this level only 2 failed to respond. One of these responded after another 0.5 unit. The other patient failed to respond to a total dose of 1 unit. She was in her fourth postpartum day.

The results obtained when 3 units of oxytocin are administered intramuscularly are shown in Table I, Group 3. This is the same dose as was used by the Newtons. Equally good results have been obtained with 2 units of oxytocin intramuscularly in 6 patients (Group 7). When 1 unit is administered intramuscularly (Group 8) some patients fail to give a positive response even though milk is present in the breasts. Thus, 2 units seems to be about the amount required for a consistent response when oxytocin is administered intramuscularly.

Complications

Only one patient complained of a uterine contraction following any of these injections of oxytocin or oxytocin-S. This one patient had received 0.5 unit of oxytocin-S on the fifth postpartum day. No other complications or side effects were observed.

Comment

The data presented herein show that oxytocin isolated from the posterior pituitary gland and the synthetic oxytocin described herein as oxytocin-S have milk-ejection activity in the human being and that these agents used for this purpose have no observable side effects except for the occasional contraction of the uterus when the oxytocin is injected after the third postpartum day. The milk-ejection activities of the naturally occurring isolated oxytocin and the synthetic oxytocin, as tested here, are identical. The fact that the synthetic oxytocin has milk-ejection activity indistinguishable from the oxytocin isolated from the posterior pituitary gland proves that the compound oxytocin has both oxytocic and milk-ejection activity inherent in its molecular structure.

The ejection of milk from the breast or breasts of these patients after the injection of oxytocin varies widely, from the showing of a bead of milk at one breast to the actual ejection of a stream of milk for a distance of 1 to 2 cm. from the nipples. The great majority, however, responded with a dripping of milk either from both breasts or from the breast to be used for the approaching feeding. This flow of milk was generally transitory, lasting generally for less than 1 minute. When the baby was put to breast shortly thereafter the mother usually reported that the baby was able to obtain milk with what appeared to be and felt to her like less effort than previously.

These data, combined with those already presented by Newton and Newton[9] (1951), strongly suggest that the milk-ejection property of oxytocin warrants more of a clinical trial as a therapeutic agent than it has had to date.

Summary

1. Oxytocin isolated from the posterior pituitary gland free of any detectable amount of vasopressin and by available physical and chemical criteria essentially a pure chemical compound has milk-ejection activity in recently parturient women who have milk in their breasts.

2. A synthetic octapeptide amide, in so far as has been tested, indistinguishable from naturally occurring oxytocin in other properties, has milk-ejection activity in similar puerperal women indistinguishable from the naturally

occurring oxytocin, thus affording conclusive proof that oxytocin has both oxytocic and milk-ejection activities inherent in its molecular structure.

3. Milk ejection occurs consistently in these women when approximately 0.5 unit of oxytocin is administered intravenously, or when 2 units of oxytocin are administered intramuscularly.

References

1. Cross, B. A., and van Dyke, H. B.: J. Endocrinol. **9**: 232, 1953.
2. Ely, F., and Petersen, W. E.: J. Dairy Sc. **24**: 211, 1941.
3. Folley, S. J.: Brit. M. Bull. **5**: 1100, 1947.
4. Gavin, W.: Quart. J. Exper. Physiol. **6**: 13, 1913.
5. Livermore, A. H., and du Vigneaud, V.: J. Biol. Chem. **180**: 365, 1949.
6. MacKenzie, K.: Quart. J. Exper. Physiol. **4**: 305, 1911.
7. Newton, M., and Newton, N. R.: J. Pediat. **33**: 698, 1948.
8. Newton, N. R., and Newton, M.: Pediatrics **5**: 726, 1950.
9. Newton, M., and Newton, N. R.: Am. J. Obst. & Gynec. **61**: 664, 1951.
10. Ott, I., and Scott, J. C.: Proc. Soc. Exper. Biol. & Med. **8**: 48, 1910-11.
11. Petersen, W. E.: Physiol. Rev. **24**: 340, 1944.
12. Pierce, J. G., Gordon, S., and du Vigneaud, V.: J. Biol. Chem. **199**: 929, 1952.
13. Popenoe, E. A., Lawler, C. H., and du Vigneaud, V.: J. Am. Chem. Soc. **74**: 3713, 1952.
14. Schäfer, E. A.: Quart. J. Exper. Physiol. **6**: 17, 1913.
15. Schäfer, E. A., and MacKenzie, K.: Proc. Roy. Soc., London, s.B **84**: 16, 1911.
16. Turner, C. W., and Cooper, W. D.: Endocrinology **29**: 320, 1941.
17. Turner, C. W., and Slaughter, L. S.: J. Dairy Sc. **13**: 8, 1930.
18. Turner, R. A., Pierce, J. G., and du Vigneaud, V.: J. Biol. Chem. **191**: 21, 1951.
19. du Vigneaud, V., Ressler, C., Swan, J. M., Roberts, C. W., Katsoyannis, P. G., and Gordon, S.: J. Am. Chem. Soc. **75**: 4879, 1953.
20. du Vigneaud, V., Ressler, C., and Trippett, S.: J. Biol. Chem. **205**: 949, 1953.
21. Waller, H. K.: Lancet **1**: 69, 1943.
22. Whittlestone, W. G.: J. Endocrinol. **8**: 89, 1952.
23. Whittlestone, W. G., Bassett, E. G., and Turner, C. W.: Proc. Soc. Exper. Biol. & Med. **80**: 191, 1952.

RELAXATION METHODS IN LABOR

A Critique of Current Techniques in Natural Childbirth

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SINCE Grantly Dick Read announced the application of relaxation methods to labor, interest has been manifested by the growth of a considerable literature on the subject. According to Read[1] and various others who have engaged in the field, these methods derive from the physiological investigations and the clinical techniques which originated in this Laboratory. While Read's system, in addition, admittedly includes several approaches aside from relaxation methods, he has stated that his objectives in childbirth were achieved only after he learned of the physiological procedures which I developed and which he began to apply in his practice. The present article has the following objectives: (1) to clarify the underlying physiology of the subject; (2) to point out the necessity of scientific tests of the training methods employed; (3) to attempt to indicate more accurately what are the most effective physiological methods to be applied during labor; (4) to expose possible errors and pitfalls; (5) to help the obstetrician to achieve a better result in his patients rather than merely to gather statistical data for purposes of comparison with previous investigations; and (6) to illustrate briefly by case histories the application of strictly physiological methods as employed experimentally during deliveries prior and subsequent to the application elsewhere of relaxation methods in labor.

Believing that the expectant mother should be approached from new standpoints, the genius of Read led him at first to try for the "elimination of fear" during pregnancy through the cultivation of faith, enthusiasm, and education concerning the phenomena of labor. He reported benefits from these psychological procedures and today in perspective we might compare them with the spiritual encouragement commonly offered by religious teachers to those suffering from trial and misfortune as well as with the exhortations offered by commanders in the field to their followers. While regarding these psychological approaches as a definite advance and without belittling or abandoning them, Read[2] has related that in his experience they proved insufficient and that he failed to effect the relief which he sought from fear and pain until he resorted to our methods of physiological relaxation.

In the light of long experience with these methods, it seems safe to state that the procedures employed by Read and others toward relief from fear states and pain during childbirth can be simplified and rendered more direct and more effectual. Simplification will make it possible to test the methods employed, if restricted to physiological training alone, so that strict clinical and also scientific standards can be satisfied.

The practitioner can limit his teaching during pregnancy to physiological technique, omitting all attempts to cultivate faith, enthusiasm, and suggested states. Likewise he may omit detailed education on the mechanics of birth. Even so, if physiological training is applied strictly, there is every reason to assume that the comfort of women in labor can be furthered to a greater extent. Experience of professionals in other fields of physical training, including golf and tennis, tends to bear out the presumption that careful technical training is the one and only essential to the development of skill. However, we raise no question here concerning diet, medication, daily exercise in the open air, when possible, or concerning routine and other physical and laboratory examinations. Regardless of the regime which any obstetrician may prescribe for his patient in other respects, we propose to examine the results secured when attempts to influence the pregnant woman by psychological and psychiatrical influences are altogether omitted, aside from the results of relaxation training alone, as performed according to scientifically tested standards. Evidence will be presented below, if such evidence is really needed, that when the expectant mother is sufficiently relaxed during labor, thereby with less nervous apprehension and with less pain, she will as a rule take full joy in the birth of her child, while she remains conscious to appreciate the moment, without any necessity on the part of the obstetrician to inculcate appropriate emotions.

Methods

If nervous and mental training during pregnancy is to be limited to relaxation methods alone, these methods and their purposes need to be set forth with precision. Aiming to lessen suffering, various clinics in this country as well as abroad have sought to apply relaxation methods, taken as a rule from my early texts[3] and more or less modified according to the views and habits of each individual worker.

Our investigations throw light on the resultant "relaxation exercises" which have been prescribed in various manuals for the expectant mother as well as in texts for other types of patients, some written by physicians, others by laymen, but all as a rule more or less deriving from my earlier texts. Although these texts contained no "relaxation exercises," some misunderstanding has arisen, evidently in consequence of the instructions therein to contract each of most of the principal muscle groups of the body on successive occasions. Our purpose in these instructions is as follows: (1) to afford the patient the opportunity to sense and thus to learn to recognize contraction, i.e., tense states, in each and every locality (a) under favorable conditions (free from nervous states and from pain), in order that later on she might become able to recognize contraction (b) under unfavorable conditions (during nervous disturbances and perhaps pain); (2) by repetition of these contractions while she observes the muscle sensation, to cultivate an increasing ability to perceive and to report finer shades of muscular contraction or tonus likewise (a) under favorable and (b) under unfavorable conditions; (3) by further repetition of these contractions and of the concomitant observation, to render it habitual for the patient to take note of how tense she is in any locality, until it becomes automatic, i.e., "second nature," to do so, requiring little or no active attention, both (a) under favorable and (b) under unfavorable conditions.

By these procedures the patient learns to observe when and where she is tense, but they are not designed to teach her to relax. This is a purely negative process, a not doing, which obviously can never be effected by means of exercises, contractions, which are positive. Accordingly, in order to bring about the desired state of learning to go negative, as it is called, special instructions need to be added to the foregoing type. Having observed what she does when she contracts each muscle group, she is requested *not* to engage in this act farther, whereupon, following trials and repetitions which vary with each individual, sooner or later she learns to let the muscles go. Accordingly, in outline, the patient is trained both in quick and in slow progressive relaxation, generally one per day of many or most muscle groups. Aided by practice at home by herself, she gradually learns to relax visible, gross muscular contractions (a) under favorable conditions and (b) under unfavorable conditions. Thereafter, if she has learned to recognize finer contractions, of the type invisible to the naked eye, but definitely measurable, she is prepared for instruction in relaxing such residual tensions (a) under favorable conditions and (b) under unfavorable conditions. With continuing repetition, during both instruction and practice periods, she tends to form habits (1) of being able to observe when and where she is tense, even in slight degrees; (2) of being able to relax tension states under both favorable and unfavorable conditions by quick and by slow progressive relaxation; (3) of maintaining a more relaxed state than previously was her wont without the necessity of paying attention to her parts. Thus she tends to acquire a lowered tension level, as compared with previous states of possible irritability and excitement, but, in addition, she has been trained to meet conditions of stress by direct observation of her reaction attitude and the introduction of proper self-controls.

The training of the pregnant woman can be limited to the lying posture, while in later stages she assumes positions appropriate to delivery with legs bent at the knee, being taught to relax the abdominal muscles extremely, or to contract them for purposes of expulsion, at the same time keeping most other muscles relaxed. (In other classes of patients, advanced forms of training are given with the patient sitting more or less erect; and, finally, while reading or engaging in other occupations. This is known as differential relaxation.)

The doctor who carries out these teaching methods cannot be sure of what he is effecting merely by observing the patient's appearance and behavior as she reclines or sits; in addition, I learned, he must apply strict methods of physiological test. Thereupon, we find that teaching the beginner to recognize when and where she is tense at any moment, whether transiently or steadily, is a necessary, but only a preliminary, step toward the acquisition of technical skill in relaxation. Many people assume without ground that they know when they are tense or relaxed although they never have been taught to recognize their muscular states. These include individuals who assert that they are quite relaxed while driving or while playing golf or while listening to certain music. Such claims have not been supported in my experience when tested by laboratory methods: they confidently state that they are "relaxed" at a time when electromyographs generally indicate to the contrary. Not only as a rule are the people mistaken who assert that they can tell whether they are tense or relaxed without preliminary training to observe; likewise, they generally prove to be mistaken if they claim that they can relax, i.e., reduce tonus toward zero, with no preliminary training in observation. At times some succeed, but only transiently, as a rule, being unable to maintain a relaxed state even under favorable conditions, in the absence of ability to recognize whether a part really is relaxed.

Accordingly, the beginner following my instructions bends her left arm steadily for several minutes in order to evoke the muscle sensation in the left biceps-brachial group for her to observe carefully.

Careful training for labor requires that the patient be taught to recognize the presence of muscular contraction anywhere over the body, no matter how slight. After she has reported that she recognizes contraction in the muscle group, such as the left biceps-brachial group, with which we begin, she is shown how to relax the group extremely. This is to be done with almost all of the noteworthy muscle groups in the entire body, if time permits. If not, some of these groups are omitted in shorter courses of training, but as a rule a lesser degree of skill can be expected to result. In any event, the patient learns to recognize contraction in various parts in a certain order. The large muscle groups are observed first, because the sensation therefrom is most conspicuous. As she relaxes a given part, she *simultaneously* relaxes all parts that have received practice previously. The order most often used is: left biceps, left triceps, left hand extensors, left hand flexors, right upper limb in similar order, left foot extensors, left foot flexors, left leg extensors, left leg flexors, left thigh flexors, left thigh extensors, right lower limb in similar order, abdominal muscles, erectores spinae, respiratory muscles, left pectoral group (forward extension of arms), right pectoral group, left and right interscapular groups (backward movement of shoulders), elevators of shoulders, bending head to left, to right, forward, backward, holding it up stiffly, wrinkling the forehead, frowning, closing eyelids tightly, with eyelids closed lightly, turning eyes to look toward left, right, up, down, straight forward. Practice is given until the patient comes by her own observation to be able to note the eye tensions which occur upon visual imagery of every variety. Later come speech tensions, including closing the jaws, opening the jaws, smiling (cheek muscles), rounding the lips to say "O," protruding the tongue, retracting the tongue, counting 1 to 10, imagining counting 1 to 10 and other acts of imagined speech. Thereafter the patient is trained to observe what takes place in her musculature upon the entrance of the physician or when disturbed in any manner. In the course of training, she applies the skills she has learned to observing what takes place during any emotional states which may chance to occur. After recognizing the tensions then present, she is practiced at relaxing them. Limits of space preclude more than the barest outline of the physiological techniques indicated. The general purpose is (1) to teach the patient to observe when and where she reacts with skeletal muscle contraction and (2) to instruct her to relax her muscles and to maintain a highly relaxed state during labor. Practice is given not only at quick relaxation (and recordings show that a skeletal muscle group in gross contraction can be relaxed often within a fraction of a second) but also at slow progressive relaxation of various parts, in order to do away with residual tension. The aim is to achieve diminution of pain reaction and of suffering, rather than complete analgesia such as is accomplished by ether and similarly acting anesthetics.

Like other contractions, bending the left arm is not performed as an exercise to induce a state of relaxation in that group, as often has been the aim in articles and books based upon my tests in their employment of "relaxation exercises." Without doubt, exercises in muscular contraction can prove of use toward developing muscle and toward promoting circulation; if so employed, we can have no objection; but contractions as often employed in obstetrical training obviously will not tend to fulfill the three aims enumerated above. My aims are to have the patient contract a part in order

to show him what *not* to do, if he is really to relax there. In contrast with these aims, "relaxation exercises," as often prescribed, seek to attain relaxed states directly through exercises. Tests in my Laboratory have failed to make it likely that efficiency in relaxation can be cultivated directly through any form of exercises whatsoever. I have found that contraction of any particular muscle group is not characteristically followed by enduring or by progressive relaxation in that group or elsewhere. Furthermore, if exercises really were capable of inducing advanced states of relaxation, we should expect athletes, teachers of physical education, and sport coaches to be experts. On the contrary, when examined with electrical instruments, these types, like other untrained individuals, failed to be able to relax extremely and to control their muscular states until they received the training outlined under the three captions mentioned above. The only difference from most other individuals was that they tended to learn a little more quickly.

Exercise in nervous persons often tends to aggravate their symptoms, in contrast with measured relaxation, which, if carried sufficiently far, invariably diminishes them, at least as long as the relaxed state endures. In my experiences with relaxation exercises, the degree, extent, and duration of resultant measurable relaxation as a rule falls short of being sufficient to accomplish most effectively the clinical ends of reducing nervous irritability and excitement. Accordingly, relaxation exercises evidently are not the best pedagogic means of enabling the pregnant woman to reduce her irritability to the point where fear, apprehension, and pain sensibility become notably diminished.

Although the "relaxation exercises" prescribed in various manuals for the expectant mother have never received physiological testing and validation, nevertheless, they have been reliably reported to result in many easier labors. Obviously, any and every given practice proposed to train the patient to relax should first be examined by critical scientific testing measures.

Evidence secured by such measures has never been presented that the following types of exercises are really efficient in relaxation training: breathing exercises of various kinds, including those in which the patient lies with knees bent and feet on the floor; flexing or extending one or more limbs, with or without holding some position thereof; pressing the head back, forward, or in any other direction; opening and closing the mouth; squatting; polishing the floor on hands and knees; rocking the pelvis; turning the spine in one direction or another, or otherwise engaging in twists or contortions. From a physiological standpoint, there is no reason to expect these and other forms of exercise to promote the ability to relax to an extreme degree when under conditions of stress. After any exercise, I have found upon test, relaxation does not as a rule proceed to the point of absence of residual tension, which degree is required for best results during labor.

Physiological Tests of Relaxation

Precise tests of states of contraction and of relaxation have been made possible by advances in electromyography and in what I have termed electroneuromyometry.[4]

The medical student first becomes acquainted with nerves and muscles in isolated preparations made from laboratory animals. He learns that the one and only act performed by living muscles is contraction and that the diminution of this state is properly termed "relaxation." Muscular relaxation is the lengthening of fibers effected internally, without any application of stretching force.

In the intact organism, muscular contraction and relaxation never occur in isolation. When a muscle contracts, the afferent and efferent nerve supplies necessarily are active at the same moment, while impulses proceed in divers and multitudinous circuits back and forth in the autonomic nervous system, in the spinal cord, and in the brain. The rates of these impulses can be on the order of 40 to 100 meters per second, as they pass to and fro. Thus muscular contraction occurs only as a portion of a most intricate set of physiological processes, which may be indicated thus: muscle ↔ peripheral nerves ↔ cord ↔ brain.

In preparation for obstetrics as well as for all other departments, the medical student should be taught that, when a muscle contracts, wire electrodes placed at any two points therein record a difference of potential[5] which varies with the magnitude of contraction, though not proportionally. Employing apparatus developed in this Laboratory (aided by the Bell Telephone Laboratories), I have shown that the slightest contractions in intact man can be electrically measured with precision, with an error of only (approximately) 0.25 millionth of a volt (¼ μv). Direct measurements can now be made of nervous, muscular, or neuromuscular activity by photographic and by pen recordings; in addition, the integrating neurovoltmeter (likewise developed here) has made it possible to take daily measurements of such states even without resort to photography or pen recordings (Fig. 1).

By these means it has become possible to investigate basic physiological problems concerning muscular states and their relations to mental activities, so that past vagueness and theories concerning the "mind" now for the first time in history can be replaced by hard facts. Investigations have included states of fear and of pain, thus bearing upon relaxation training for childbirth, and these have been carried out over the past twenty-five years, during which period thousands of recordings have been made in various fields of human disease as well as in health. Evidence has been accumulated as to the nature of states of fear and apprehension which can in part be summarized as follows:

When any individual, including the pregnant woman, suffers a spell of fear, apprehension, or of severe pain, an increase of action potentials is recorded as a rule from any and every skeletal muscle in which electrodes are inserted. Obviously, similar increases are recordable if the electrodes are inserted directly into peripheral nerves instead of into muscle. This increase is conspicuous and requires no statistical methods for confirmation, being evident to the naked eye of the physician who can watch the indicator on a dial mark up the increase shown at any instant. Commonly I employ four channels of simultaneous record, for example, one from arm muscles, a second from thigh muscles, a third from eye-region muscles, and a fourth from jaw muscles. Thus the physician can continuously follow the indicators of the neuromuscular tension in each of these four (or other) representative regions, while the technician (employing a slide rule to reinterpret the shifts of a beam of light from a d'Arsonval galvanometer) sets down the values of the

action potentials averaged in voltage over two-minute intervals, which afterward are plotted in a graph showing the patient's nervous state during the period.

Under these conditions, if the patient relaxes his musculature (particularly including that of the eye and speech region) to a very marked extent, (1) any visible signs of emotional disturbance obviously cease and the trained observer notes the change conspicuously, while concurrently (2) action potentials diminish accordingly, and (3) the patient reports a diminution or even the complete absence of the emotional state, so long as the marked reduction of action potentials persists.

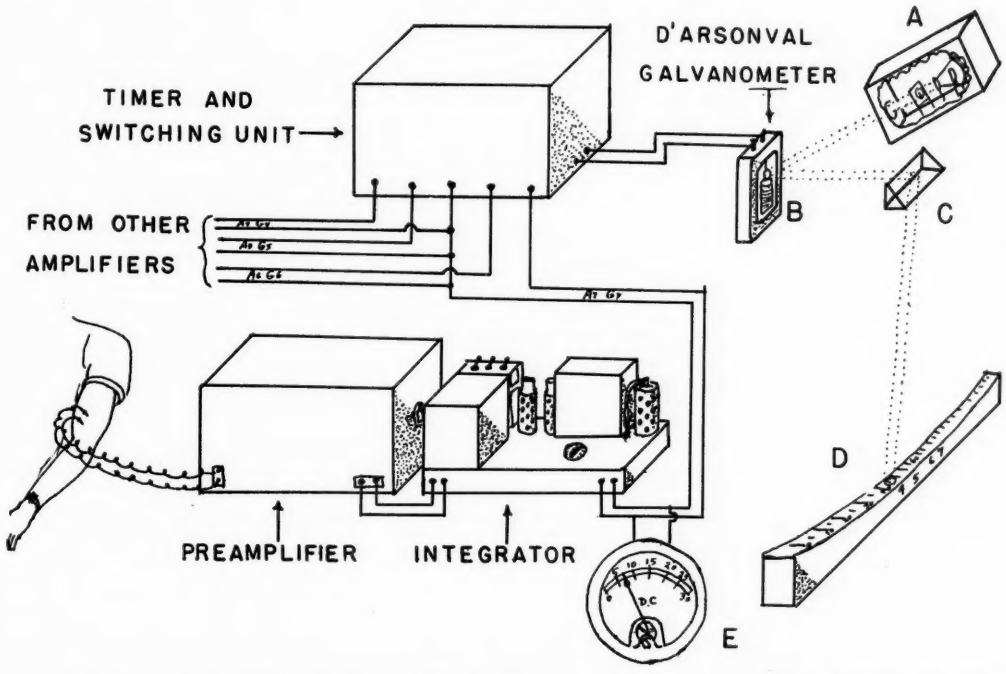

Fig. 1.—A pair of fine platinum iridium wire electrodes penetrate the left biceps-brachial muscles (three other pairs simultaneously in three other selected regions not illustrated). Upon contraction, phasic or steady, in the tested muscle group, potential differences in the electrodes vary with the degree of contraction. These voltages are amplified and rectified and then charge a condenser. Every two minutes this charge is measured as follows: The condenser is discharged by means of a timer and switching unit periodically through a d'Arsonval galvanometer with an attached mirror (*B*). Light from a source (*A*) is reflected first to this mirror and then to a prism (*C*), and then on a scale (*D*). Thus a spot of light moves on the scale and returns to zero. The extent of this movement is standardized in terms of microvolts with a calibrating unit. Employing a slide rule, the technician records the averaged microvoltage for each muscle group at the end of every two-minute interval of test. Four meters, like *E* in the illustration, indicate the fluctuations of neuromuscular tension to the observer at every instant of time. In a tense or emotional person, when tested, the indicators are seen to fluctuate and to remain at high values. In a patient adequately trained for labor such fluctuations are diminished or largely absent. The indicator remains at or near zero for most or all of the test.

Investigations on the electrophysiology of mental activities have made it clear why extreme muscular relaxation directly quiets emotional as well as sensory and perceptual states.[6] In suitably controlled studies, it was found that when an individual imagines that he is performing an act, he actually performs the act in appropriate muscles but in so extremely reduced a manner and so swiftly that the most sensitive equipment is required for

detection and registration of the neuromuscular processes which are engaged in addition to the brain processes. In each and every act of imagination, there engage muscular patterns of contraction no less specific than are the brain processes. Because these contractions often are microscopic, they escaped detection prior to our investigations. The invariable occurrence of specific or unique neuromuscular processes was confirmed not only in each and every act of imagination of performance which was investigated but likewise in the imagination of abstract matters as well as in emotional states and in all other forms of mental activity investigated up to date. Proof that the neuromuscular pattern occurring uniquely during each and every mental activity is not merely an accompaniment or peripheral expression of the brain process assumed to be present was afforded, for when absence of the specific neuromuscular pattern was brought about by whatsoever experimental means, the mental act itself was deleted, even though general conditions of stimulation were otherwise unaltered. For example, extreme relaxation, when it abolished the specific neuromuscular pattern, invariably deleted also the corresponding act of imagination or of emotion. Indeed, during extreme muscular relaxation, mental activity, including emotion, diminishes toward zero.

Contrary to popular belief, the brain processes which we all assume to condition each and every mental act have never been identified by electroencephalographers or by other physiologists. It is even conceivable that mental activities are not uniquely determined by brain circuits alone, but only by the neuromuscular patterns, at least to some extent. At any rate, the unique relationship *has* been determined in the case of neuromuscular patterns.

Thus every type of mental act evidently includes not only a hypothetical (probably specific) brain process but also a demonstrable specific neuromuscular transient pattern.

Thus the traditional belief that ideas and emotions exist primarily in the brain or mind was once and for all exploded. However, outworn views often persist obstinately even in medical journals; we still read about muscular states as "expressions of the mind." According to these outmoded views, "ideas first exist in the mind," and thinking goes on by means of closed circuits within the brain; later thoughts and emotions are "expressed" in muscular contractions. From this false premise, when regarded as firmly established fact, the uninformed writer assumes that change of muscle states cannot really influence emotion, including fear, or really influence perception, including pain; and he may even jump to the conclusion that when mental activities diminish upon progressive relaxation, the result is produced by what he calls "suggestion." We can readily understand why any writer, basing his views on beliefs which prevailed prior to present-day investigations, should thus wrongly attribute certain effects of relaxation to "suggestion." However, experimental psychologists and experts on suggestion have avoided this pitfall.

Psychiatric suggestion evidently plays no part in the reduction of mental activities at the moment of progressive muscular relaxation, for (1) suggestions and prophecies and reassurances are carefully avoided; (2) in control tests, where for experimental purposes suggestions and reassurances are offered, action potentials often persist instead of declining while the patient remains emotional and reports so; (3) in hypnoidal states, the patient told to relax further may instead show an increase of action potentials, contrary to the efforts of the hypnotist and contrary to the claims made by the patient that he feels more relaxed. Indeed, hypnosis cannot be relied upon to produce relaxation, being characterized often by increased action potentials and by persistence or increase of knee jerk, in contrast with physiological relaxation methods, wherein, as stated, the opposite prevails.

From what has been said previously, it follows that patients trained to relax residual tension show no resemblance to being in trance states during labor. They can think for themselves and can talk like any other person; but while doing so, they are not sufficiently relaxed. In some current accounts, the enthusiastic comments made by patients in labor make it obvious that during such moments they are by no means relaxed. Enthusiasm and extremely relaxed musculature are incompatible at one and the same instant. Subsequent to successful relaxation, however, enthusiasm may be manifested, as will be illustrated below.

Something more needs to be said about the mental activity of patients under training to relax. As stated above, I have shown that all forms of mental activity, including reflection and emotion, involve more than closed circuits within the brain and nervous system, as was generally believed prior to these investigations. It is established that the skeletal muscle system invariably participates in each and every mental act as differentially as do the brain and other sections of the nervous system. The patient (during labor or at other times) whose action potentials from the eye and speech regions measure near zero is not reflecting at the time. We do not find, as one author states, that the waking mind is always active or that "it is impossible not to think about something when you are awake." If that were true, relaxation methods would be less worthy of application to labor. If the instructor fails to teach his patient to relax sufficiently so that for the time being reflection and all forms of emotion effectively decline, he has not accomplished what is possible.

Once again, however, it is necessary to emphasize that the patient is not to be told in advance that her mental activity decreases upon extreme relaxation. On the contrary, she finds this out for herself, if advance hints and information are omitted, giving her full opportunity to learn to observe for herself and to gain independence in controlling her musculature. Between labor pains, the well-trained patient ceases to be mentally and physically active and will sleep, even if only for a few seconds, when muscular contractions of the eyes and speech approach zero, as shown by the lowered levels of action potentials.

Comment

The considerations outlined above throw light upon certain controversial questions which have been raised recently. Mandy and associates,[7] writing apparently under Freudian orientation, imply that the trainer appears to the patient as a father surrogate, imparting influences which they insinuate may be detrimental psychiatrically. One such successful candidate whom they conducted through natural childbirth had been found by a psychiatrist to be his "best hypnotic subject."

If Mandy and co-workers practiced on a patient frequently hypnotized, their success with this patient may very well (as they contend) have rested on the employment of suggestive measures rather than upon strict measures of relaxation training conducted with a view to avoiding suggestive measures. In my Clinic a patient previously frequently hypnotized is readily distinguished from others and attempts to train her (or him) to relax are promptly discontinued. She does not learn to relax, but tends to fall into a trance state. Contrary to the belief of Mandy and his collaborators, highly suggestible subjects make the poorest pupils for relaxation training.

Mandy and his associates quote the statement by Read that "those who have learned relaxation lay as if in a trance throughout the second stage . . .," and they conclude that "the state of relaxation in these women is indistinguishable from a hypnotic trance." However, L. Z. Freedman and others[8] sharply disagreed. They furnished evidence that, in similar cases of natural childbirth, the state of relaxation was definitely distinguishable from a hypnotic trance by a classic mode of differentiation. They regarded the absence of gross amnesia as conclusive evidence against the theory that Read's is a "hypnotic" technique since other studies have reported amnesic residue invariably following delivery under hypnosis.

If we accept Freedman's conclusion, it may be that Read made an unfortunate choice of words in likening the condition of his patients during labor to a trance state. Doctors and psychologists, including some of Freudian orientation, have been free to examine patients in my Clinic at all stages of relaxation training and have found no similarities to trance states. On the contrary, they talk gladly with any examiner and obviously are free from undue suggestibility and from other so-called father surrogate influences. I have not examined Read's patients and have not applied requisite testing methods. However, it is important to note the following: (1) Methods of suggestion and hypnosis, as is well known to experienced psychiatrists, have proved notoriously unreliable for the production of analgesia in most individuals. It can be safely prophesied that history will repeat itself wherever they are being used for such ends in obstetrics and that they will be discarded if only for the reason that they have proved effective in producing analgesia at most only in about 10 per cent of patients. (2) The hypnotized patient and the patient in any form of hypnoidal trance may believe that he is relaxing and the doctor may concur; but adequate electromyographic tests disclose the contrary, as has been shown in my Laboratory.

Case Reports

Historically the first patient to receive relaxation training in any form during pregnancy came to labor in the Lying-in Hospital of the University of Chicago, Sept. 23, 1930, under Dr. Fred Adair. She was a primipara, in good health, and I attended the delivery along with Adair. What was most noticeable to onlookers, who included Joseph DeLee, was her apparent emotional quietude, the absence of moans and groans during the first and second stages of labor. As long as labor contractions were separated by a considerable interval, she was ready to converse during such intervals, but she made her remarks brief and would not tense herself sufficiently to answer any questions which, being ill timed, were directed to her during contractions. When contractions evidently became more frequent, she maintained relaxation continuously. This self-direction was carried on without suggestion from the doctors. There was no resemblance to a trance state at any time.

Being entirely unfamiliar with relaxation methods during labor, neither Adair nor his associates were prepared when the head appeared at the introitus and an associate performed the delivery, employing an anesthetic in the final stage. Only when the patient thus was rendered unconscious and unable to control her muscular state did she emit complaint and then in the form of the familiar shriek. On the following morning she sat up in bed, laughing and in the best of spirits, evidently relatively free from any fatigue or exhaustion.

These results were had with physiological training methods alone, without resort to endeavors to cultivate enthusiasm or to appease fears or to educate her in the mechanics of childbirth. It is suggested that physiological methods alone will suffice.

Since 1930 approximately ten other instances of pregnant women trained for labor by relaxation methods alone have shown essentially similar results. One such instance follows in illustration:

The patient, 28 years of age, employed as a statistician, had before marriage complained of various nervous states, including anxiety about her health. Her father suffered from coronary disease and this was one source of her fears. Clinical and laboratory examinations proved approximately negative. As she learned to control her musculature, her anxiety lessened and practically disappeared. There was now nothing to detract from her happiness after marriage. She had secured a superior position in industrial statistics while at the same time continuing her studies toward a master's degree, when she began to have fears that her intellectual career was threatened by conception, notwithstanding precautions to the contrary; and when these fears gave way to certainty she became emotionally disturbed. However, within a few months she learned to observe the muscular states present whenever she engaged in emotional concern and with daily practice she acquired habits of control and thus gradually adapted herself to the interruption of her career and became happy once more. These satisfactory adjustments were effected without any attempt at argument, persuasion, or other psychiatric influence, since these approaches can be omitted, if the patient really learns to observe and to relax.

In Fig. 2 is shown a graph of her tension states during a test on Aug. 26, 1952, the last date of treatment prior to her delivery about three months later. She had married a physician, to whom I am indebted for the following account, including her own notes:

The patient, a 28-year-old white woman, gravida i, was admitted at 8:25 P.M. of Nov. 21, 1952, to the labor room of Michael Reese Hospital. The attending physician was Alex S. Tulsky. Pertinent history and findings were as follows: pains were occurring every 8 to 9 minutes starting at 6:00 P.M. of the same day, the bag of waters intact;

blood pressure was 125/80; temperature 98° F.; pulse 72; respiration 18; fetal heart beat 116, of good quality. Examination of the abdomen revealed the breech to be in the fundus with a right occipitoanterior presentation at 40 weeks' gestation.

Labor continued uneventfully. A soapsuds enema was given at 9:45 P.M. At 10:15 P.M. the patient's contractions were 3 to 4 minutes apart, lasting 25 to 35 seconds. The fetal heart tones were 120.

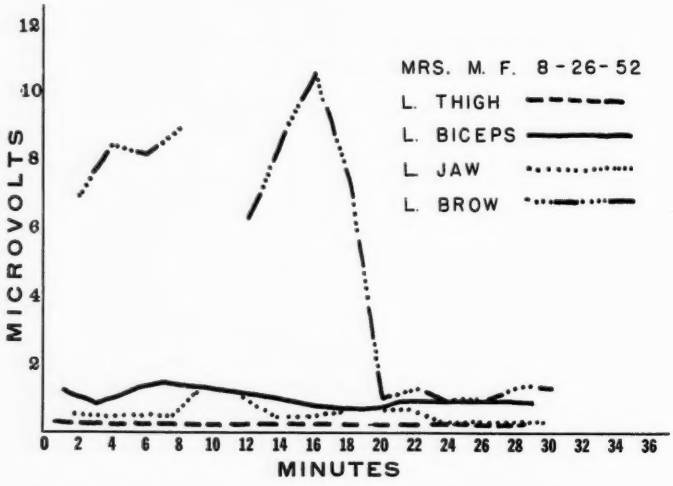

Fig. 2.—Recordings of action potentials from four representative neuromuscular regions in a primipara at the close of the training period, shortly before delivery. Twenty minutes elapsed until she relaxed her brow sufficiently to bring action potentials below one microvolt; but, from the outset, those from the jaw region were below one microvolt (an excellent performance), while those from the arm region were below this value persistently following the seventh minute. Throughout the record, the thigh muscles registered as if there was complete relaxation. A record of this type affords graphic evidence that the patient is fairly prepared really to relax during labor, but obviously offers no certainty that she will then perform efficiently. (This patient was relatively slow to acquire skill; lower records from trained individuals are common.)

At 11:15 P.M. contractions were timed at intervals of 3 to 5 minutes and were moderately strong, lasting from 30 to 40 seconds.

At midnight the contractions were approximately the same as above as to time and duration. The fetal heart tones were 128.

At 1:00 A.M. the contractions came every 3 to 4 minutes with a duration of 45 to 50 seconds. At this time the membranes ruptured spontaneously.

At 1:30 A.M. the second stage of labor began. Contractions became more frequent with the duration of the contractions 45 to 50 seconds. This continued until the delivery at 3:42 A.M. At that time a normal male infant who weighed 6 pounds, 8 ounces was delivered spontaneously. The third stage of labor lasted 4 minutes and passed uneventfully.

The duration of the first stage was 7 hours, 30 minutes; of the second stage, 2 hours, 12 minutes; of the third stage, 4 minutes. The total duration of labor was 9 hours, 46 minutes.

The patient received no medication until 11:55 P.M. at which time an intern who did not understand that the patient was not to receive medication administered 50 mg. of Demerol intramuscularly. An episiotomy was performed using pudendal block with local anesthetic. Nitrous oxide was administered intermittently in association with the last three major contractions prior to delivery. An oxytocic agent (Ergotrate) was administered intravenously following the delivery of the placenta.

The episiotomy was repaired in the usual fashion and the patient's recovery was uneventful. Following the delivery the findings were: blood pressure 130/82; pulse 72; uterus firm; total estimated loss of blood 200 c.c.

From the onset of labor the patient employed the Jacobson technique of relaxation.

During the first stage of labor, she was able to relax to the point of *sleep* between contractions. The only real pain experienced was that associated with the last few major uterine contractions at the end of the first stage. Prior to this she was relaxed and was able to sleep. At the end of the first stage she experienced some back pain. This was relieved by a few minutes of back rubbing by her husband.

It was considered, in general, that this was a rapid labor for a primipara except for the long duration of the second stage. According to the consensus of medical opinion, the main reason for the prolongation of labor was that the patient did not bear down with the contractions during the second stage as much as she could have.

She was up and about and going to the washroom within 4 hours following delivery. She was able to have a natural bowel movement on the second day following delivery. This was attributed to the absence of an anesthetic during the delivery.

Patient's Comment.—"This is a factually cold medical report of the labor and delivery of my son, Steven. It does not indicate at all the great joy that the mastery of relaxation technique afforded me. For I was conscious the entire time, had relatively little pain, and was there at the exact moment of Steven's birth. It is my opinion that mothers who are given an anesthetic at the time of the actual birth of their babies are robbed of the feeling of complete achievement and the crowning of all their efforts. The birth of the baby is the high light of the entire nine months of waiting.

"In addition, I felt fine almost immediately after the delivery and went on to a rapid recovery and to nursing the baby.

"In retrospect, I might add that some doctors who were brought into the delivery room to watch my technique evidently were surprised that I did not groan with each uterine contraction. One doctor asked me, 'Doesn't it hurt?' I replied, 'It didn't until you asked the question!' I do not know if he caught the point, which was that a person can either relax sufficiently to be relatively free from pain or answer questions; but a doctor should know that it is impossible to do both at the same time because you have to become tense in order to understand and answer questions. However, my husband thought that my reply was a little rude."

Summary

1. Technical relaxation methodology is the therapeutic application of a field of physiology based upon fundamental principles of physics, chemistry, and mathematics.

2. In the light of physiological principles, thus established, some of the methods of natural childbirth have been examined.

3. While every experienced obstetrician has seen some naturally relaxed patients who never received any training but who showed little commotion or pain during labor, there is every reason to assume that the pregnant woman can be trained for labor by strictly physiological methods more efficiently. It is unnecessary (a) to stimulate enthusiasm, (b) to cultivate faith or suggested states, and (c) to educate her in the mechanics of childbirth. These three measures can lead her to be overemotional and overreflective during labor (however pleasantly) rather than strictly relaxed. Relaxation training at best proceeds by technical instruction, in many respects like professional golf or swimming.

4. Methods of relaxation training and the progress of the patient in learning need to be controlled by specialized electromyography.

5. Such control tests have not validated the employment of relaxation exercises (as modified from my texts on progressive relaxation) although these

have been reliably reported by others to result in more comfort during labor. According to physiological requirements, exercises fail to cultivate the ability to relax residual tension which is required to accomplish better results.

6. Placing responsibility on the patient as to possible use of an anesthetic at any time is not here recommended, for this tends to stimulate efforts on her part to decide what to do. Efforts to decide, like any other efforts, may include tension states in the muscles of the eyes (to visualize the anesthetic), in the speech organs (preparatory to asking for it) and perhaps in the arms and legs (to reach for it or to get it). Accordingly, it is for the physician to determine if and when any anesthetic should be employed.

7. During labor following physiological training methods alone, the patient proceeds intelligently and with self-reliance and therefore with no resemblance to being in a trance state. No careful observer finds any evidence of increased suggestibility.

8. It is essential thus to avoid psychiatric suggestion and hypnoidal states prior to and during labor, if best results are desired. Suggestive methods are undesirable because (1) they cannot be relied upon as a rule; (2) symptoms may be concealed rather than dispelled; (3) as is well known, hypnosis generally produces analgesia in only about 10 per cent of people and therefore is unsuitable for routine use on the average patient; (4) hypnosis tends to increase personal dependence, suggestibility, and neurotic symptoms; therefore hypnosis is by no means suitable to replace analgesic drugs.

References

1. Read, G. D.: Natural Childbirth, New York, 1950, Prentice-Hall Inc.; Childbirth Without Fear, New York, 1944, Harper & Brothers.
Thoms, H., and Goodrich, F. W., Jr.: J. A. M. A. **140:** 1256, 1949.
2. Read, G. D.: Address at Chicago Lying-in Hospital, University of Chicago, Jan. 29, 1947.
3. Jacobson, E.: Progressive Relaxation, Chicago, 1938, University of Chicago Press; You Must Relax, New York, 1942, McGraw-Hill Book Company, Inc.
4. Jacobson, E.: Proc. Soc. Exper. Biol. & Med. **30:** 713, 1933; Am. J. Physiol. **107:** 230, 1934; Am. J. Physiol. **108:** 573, 1934; Am. J. Psychol. **48:** 98, 1936; Am. J. Psychol. **52:** 620, 1939; Am. J. Psychiat. **97:** 513, 1940; Rev. Scient. Instruments **11:** 415, 1940; Am. J. Psychol. **54:** 266, 1941; Am. J. Physiol. **137:** 1, 1942; J. Nerv. & Ment. Dis. **97:** 197, 1943.
Jacobson, E., Lachner, J. E., and Sinykin, M. B.: Am. J. Obst. & Gynec. **38:** 1008, 1939; Am. J. Psychol. **55:** 407, 1940.
5. Matteucci, C.: Essai sur les phénomènes électriques des animaux, Paris, 1840, Carilian-Goeury et V^{r} Dalmont.
Du Bois-Raymond, E.: On Signor Carlo Matteucci's Letter to H. Bence Jones, M.D., London, 1853, J. Churchill.
6. Jacobson, E.: Am. J. Physiol. **91:** 567, 1930; Am. J. Physiol. **94:** 22, 1930; Am. J. Physiol. **95:** 694, 1930; Am. J. Physiol. **95:** 703, 1930; Am. J. Physiol. **96:** 115, 1931; Am. J. Physiol. **96:** 122, 1931; Am. J. Physiol. **97:** 200, 1931; Am. J. Psychol. **44:** 677, 1932.
7. Mandy, A. J., Mandy, T. E., Farkas, R., and Scher, E.: J. Am. Psychosomatic Soc. **14:** 431, 1952.
8. Freedman, L. Z., Redlich, F. C., Eron, L. D., and Jackson, E. B.: J. Am. Psychosomatic Soc. **14:** 439, 1952.

THE PREDICTION AND MANAGEMENT OF OUTLET DYSTOCIA

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THE outlet as a dystocia problem had had an illustrious history. Obstetrical pioneers, as Van Deventer, de la Motte, Smellie[1] and others[2-7] recognized isolated cases of the contracted outlet. Breisky[8] was the first in 1870 to recommend its measurement; he described the intertuberous diameter and invented a pelvimeter to measure it. He also defined and recommended measuring the anteroposterior diameter of the outlet. Champneys[9] in 1884 defined and used the posterior sagittal of the outlet. Klien[10-12] suggested an outlet criterion for prognostic use in that if the intertuberous diameter were 8.5 cm. it would be necessary for the posterior sagittal to be 7 cm., and if the intertuberous were 8 cm., the posterior sagittal would have to be 9 cm. to expect normal vaginal delivery. Williams[13, 14] and later Thoms[15] in the first and second decades of this century popularized the use of the sum of the intertuberous and the posterior sagittal as a prognostic criterion. Briefly, they said that a sum of 15 cm. was borderline, above which spontaneous vaginal delivery can be expected and below which increasingly difficult forceps deliveries were necessary.

Since then other methods of estimating the outlet have been recommended. McSweeney[16] and Hanson[17] have suggested using the interpubic diameter, measuring it transversely on the pubic arch 2 or 3 cm. below the bottom of the symphysis. It usually measures 6 cm. with a borderline diameter of 5.5 cm. Bull[18] defines it as follows: draw a straight line from the central point below the symphysis to the convexity of each ramus and the distance between these two points is the interpubic diameter.

Schuman[19] and McSweeney[16] recommend measuring the pubotuberous diameter from the mid-point of the medial aspects of the tuberosities perpendicularly upward to the upper surface of the superior ramus of the pubis, usually where the pubic tubercle is situated. The average measurement is 11 to 11.5 cm. and one longer than that usually suggests a funnel pelvis.

Daniels[20] and McCormick[21] use the following: multiply the intertuberous and posterior sagittal, and then divide by 2. A normal index is 55. Between 35 and 55 there is the possible necessity for outlet forceps; between 25 and 35 usually forceps are needed; and below 25 there is practically always obstruction.

Moir,[22] Williams,[23] and Morris[24] prefer the anteroposterior diameter of the outlet alone or in combination with the subpubic angle and interspinous diameter of the midplane.

Williams,[13] Thoms,[15] McSweeney,[16] Biddle,[25] Moloney,[26] Nicholson,[27] Ragan,[28] Hanson,[17] Pieri,[29] McCormick,[21] Williamson,[30] Cummings,[31] Stude,[32] Mengert and Eller[33] all prefer the intertuberous and posterior sagittal for diagnosis and prognosis.

Moir[34] uses a graph consisting of a correlation between the subpubic angle, the posterior sagittal and the estimated biparietal diameter.

Morris[24] determines the available anteroposterior diameter of the outlet in the following manner: plastic disks representing the fetal head are placed in the subpubic angle; the amount of space between the bottom of the symphysis and the top of the fetal head is measured (wasted space); this wasted space is plotted on the lateral x-ray of the pelvis below the symphysis; this is the anterior end point of the available anteroposterior diameter of the outlet; the posterior end point is the end of the last fixed segment of the sacrum. Williams[23] combines the available anteroposterior diameter of the outlet with the interspinous diameter for prognosis and recommends the sum of 21 cm. as borderline.

Allen[35-36] employs a variation of the Morris technique to determine the available posterior sagittal diameter. A semicircular transparency of 103 mm. diameter is placed in the subpubic angle of a Chassard-Lapine outlet roentgenogram. The distance from the bottom of the symphysis to the mid-point of the transparency represents the symphysis-biparietal diameter. This is measured. Then this distance is measured with a compass on the lateral roentgenogram placing the point of the compass on the bottom of the symphysis and with a circular motion determining where the line made in such a fashion crosses the tuberosities. Where this line crosses the tuberosities is where the anterior end point of the available posterior sagittal diameter is determined. Then the available posterior sagittal is measured from this anterior end point to the last fixed point of the sacrum. If this is less than one-half of the biparietal, then there will probably be disproportion. If this measurement is greater than one-half of the biparietal, there is no disproportion.

Bull[18] uses still another variation of this type of technique. He describes a sacropubic diameter, the distance from the end of the last sacral segment to the mid-point of the interpubic diameter. Then using transparencies of the fetal head of 98 mm. size, he has these fitted into various degrees of the pubic arch and then determines how long the sacropubic diameter must be for the 98 mm. head to pass the end of the last sacral segment.

Mengert[33] recommends a graphic portrayal of the outlet on one plane. The anterior sagittal diameter of the outlet is assumed to be 6 cm. He draws on the graph the subpubic arch keeping the anterior sagittal 6 cm. in length and using the clinical intertuberous. He then measures the posterior sagittal clinically and places the sacrum on the drawing at whatever distance the posterior sagittal is measured from the mid-point of the intertuberous. He considers the average biparietal measurements of large-, medium-, and small-sized babies to be 9.6 cm., 9 cm., and 8.6 cm., respectively. Transparencies of these three fetal head sizes are then made using the outline of a semiflexed head.

The size of the infant at term is estimated and the appropriate transparency fitted into the graph. Disproportion is determined by the transparency overlapping the bony portions of the pelvic outlet.

All of these various methods of determining outlet capacity are essentially variations of two groups of measurements: (1) the intertuberous and posterior sagittal and (2) the anteroposterior diameter of the outlet and its variations with or without the use of the subpubic angle.

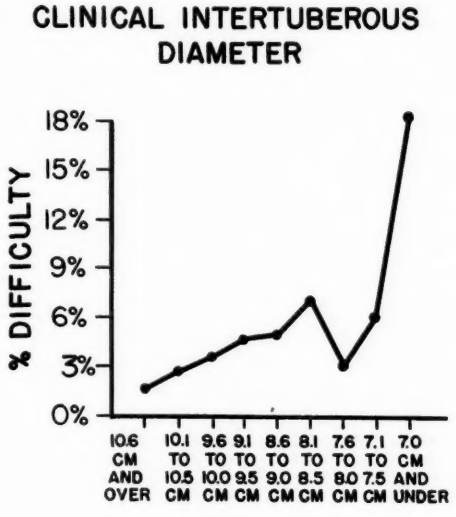

Fig. 1.

Material

The material in this study consists of those patients on whom x-ray pelvimetry has been done since July 1, 1947. Patients without pelvimetry were excluded because the correlation between clinical and x-ray measurements seemed desirable. There were 2,491 patients in whom pelvimetry had been done roentgenologically. In order to ensure that only those patients who experienced a trial of labor at the outlet in average-sized babies were included, the following groups of patients were eliminated: (1) all patients who had been delivered by cesarean section except for outlet contraction after labor; (2) all abnormal presentations such as breech, transverse lie, etc.; (3) all patients delivered by midforceps, midforceps being defined as an application on a fetal head in which the presenting part has not reached the perineum, but when the biparietal diameter has traversed the inlet; and (4) patients with infants weighing below 2,500 grams and above 4,000 grams. Thus the material consists of all vertex deliveries in which labor has proceeded to full dilation of the cervix, and has terminated either spontaneously, by low forceps, or by cesarean section in infants weighing between 2,500 grams and 4,000 grams. These patients were then analyzed in the following manner: the various basic yardsticks for determining outlet contraction were correlated with the percentage of difficult deliveries. Difficult deliveries were defined as those in which (1) excessive traction was necessary to consummate vaginal delivery; (2) if rotation was indicated, difficulty in rotation was encountered; (3) cesarean section was done after full dilation of the cervix because of lack of progress in the second stage with good contractions, with or without attempts at

forceps delivery; and (4) patients in whom the infants showed evidence of intracranial hemorrhage, whether the infant was discharged from the hospital alive or dead.

The Clinical Intertuberous Diameter

The clinical intertuberous diameter was examined first in the manner previously described at 0.5 cm. levels. Table I and Fig. 1 show the results in 1,552 patients. It should be noted that in this particular type of analysis when the diameter becomes smaller one should expect increasing difficulty. This in general is true, but there is no statistical difference between 7.5 cm. and 11 cm. in our patients. The incidence of difficulty rose sharply when the intertuberous was 7 cm. or less, but even then one could expect vaginal delivery without difficulty 4 out of 5 times and the difference between the incidences of difficulty at the 7.5 cm. and the 7 cm. levels is not statistically significant.

TABLE I. CLINICAL INTERTUBEROUS DIAMETER

MEASUREMENT	EASY DELIVERIES	DIFFICULT DELIVERIES	TOTAL DELIVERIES	PERCENTAGE OF DIFFICULTY
7.0 cm. and under	18	4	22	18.2
7.1-7.5 cm.	47	3	50	6.0
7.6-8.0 cm.	126	4	130	3.1
8.1-8.5 cm.	197	15	212	7.1
8.6-9.0 cm.	306	16	322	5.0
9.1-9.5 cm.	285	14	299	4.7
9.6-10.0 cm.	278	11	289	3.8
10.1-10.5 cm.	107	3	110	2.7
10.6 cm. and over	116	2	118	1.7
Total	1,480	72	1,552	

The Clinical Posterior Sagittal of the Outlet

Table II and Fig. 2 demonstrate that there is no great difference between the intertuberous and posterior sagittal in the general contour of the graphs. The variations seen here between this and other tables in the total number of patients depend upon whether the diameters were measured or were measurable, whether the attending obstetrician felt that it was unnecessary to measure them, or upon the lack of prenatal care in some of these patients. There does not seem to be any great change in the clinical posterior sagittal graph until a level of 5.5 cm. is reached and as with the intertuberous this variation is not statistically significant.

TABLE II. CLINICAL POSTERIOR SAGITTAL OF THE OUTLET MEASUREMENT

MEASUREMENT	EASY DELIVERIES	DIFFICULT DELIVERIES	TOTAL DELIVERIES	PERCENTAGE OF DIFFICULTY
5.5 cm. and under	6	2	8	25.0
5.6-6.0 cm.	23	1	24	4.2
6.1-6.5 cm.	38	2	40	5.0
6.6-7.0 cm.	173	11	184	6.0
7.1-7.5 cm.	211	12	223	5.4
7.6-8.0 cm.	406	19	425	4.5
8.1-8.5 cm.	221	13	234	5.6
8.6-9.0 cm.	202	4	206	1.9
9.1 cm. and over	136	3	139	2.2
Total	1,416	67	1,483	

Sum of Intertuberous and Posterior Sagittal Diameters

One would not expect that the intertuberous or the posterior sagittal alone would be a particularly good criterion of prognosis. The sum of the intertuberous and posterior sagittal has been accepted as satisfactory in the past. Table III and Fig. 3 do not corroborate this acceptance. There does not appear to be any definite increase of difficulty with decreasing sums that could be considered statistically valid. There could be two reasons for this: (1) we cannot measure the intertuberous and posterior sagittal diameters accurately in our clinic, and (2) this type of criterion is not the best for the demonstration of outlet contraction. To test the first hypothesis those patients who had a clinical intertuberous measurement between 8.6 and 9 cm. were examined by x-ray pelvimetry and the measurements compared. Fig. 4 shows that the most frequent readings were between 10.1 cm. and 11.5 cm. with a spread between 8 cm. and 13 cm. When one adds 2 cm. of soft tissue to the clinical intertuberous diameter of 8.6 to 9 cm., making it 10.6 to 11 cm., we were correct in only slightly over 20 per cent of the cases. This indicates that we cannot measure accurately the intertuberous diameter clinically.

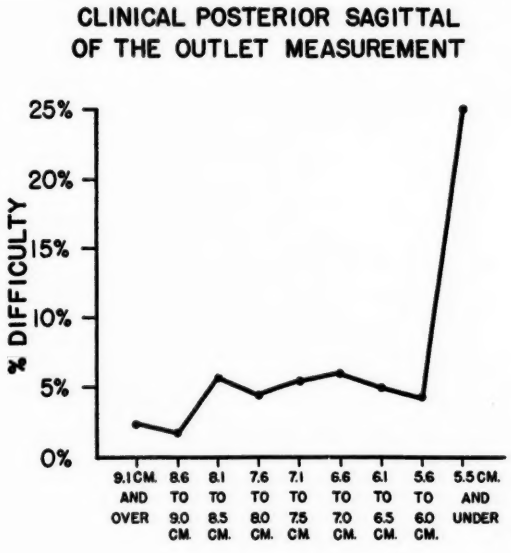

Fig. 2.

The X-Ray Intertuberous and Posterior Sagittal Diameters and Their Sums

It then seemed desirable to test the second hypothesis concerning the sum of the intertuberous and posterior sagittal diameters. The first phase of this consisted of testing the x-ray intertuberous and the posterior sagittal and their sums in the same fashion as was done with the clinical measurements. Table IV and Fig. 5 show the results with the intertuberous diameter. The curve remains essentially flat until the level of 9 cm. and under was reached, but this represents only 14 cases out of a total of 1,599. From a practical viewpoint, the x-ray intertuberous alone shows an improvement over the clinical intertuberous alone.

TABLE III. THOMS' SUM

CLINICAL MEASUREMENTS* THOMS' SUM	NUMBER OF PATIENTS			
	EASY DELIVERIES	DIFFICULT DELIVERIES	TOTAL DELIVERIES	PERCENTAGE OF DIFFICULTY
14.0 cm. and under	12	3	15	20.0
14.1-14.5 cm.	19	0	19	0.0
14.6-15.0 cm.	35	4	39	10.5
15.1-15.5 cm.	77	1	78	1.3
15.6-16.0 cm.	101	11	112	9.8
16.1-16.5 cm.	143	8	151	5.3
16.6-17.0 cm.	216	12	228	5.3
17.1-17.5 cm.	240	11	251	4.4
17.6 cm. and over	579	16	595	2.7
Total	1,422	66	1,488	

*Errors of measurement between 15.1-15.5 cm. and 15.6-16.0 cm., and between 14.6-15.0 cm. and 15.1-15.5 cm. are statistically significant. P = 98.36 and 97.92, respectively.

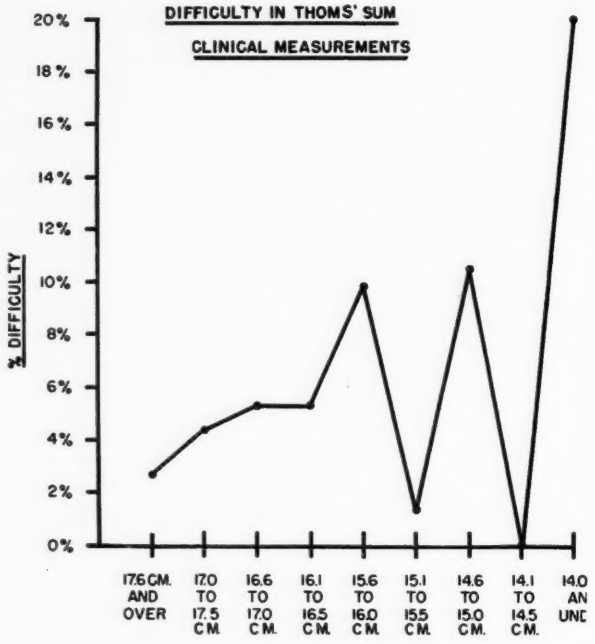

Fig. 3.

TABLE IV. X-RAY INTERTUBEROUS DIAMETER

MEASUREMENT	EASY DELIVERIES	DIFFICULT DELIVERIES	TOTAL DELIVERIES	PERCENTAGE OF DIFFICULTY
9.0 cm. and under	9	5	14	35.7
9.1- 9.5 cm.	50	5	55	9.1
9.6-10.0 cm.	136	7	143	4.9
10.1-10.5 cm.	307	18	325	5.5
10.6-11.0 cm.	330	10	340	2.9
11.1-11.5 cm.	385	13	398	3.3
11.6-12.0 cm.	182	7	189	3.7
12.1 cm. and over	132	3	135	2.2
Total	1,531	68	1,599	

When the x-ray posterior sagittal diameter was examined (Table V and Fig. 6), the general curve was better than the x-ray intertuberous except for

those cases in which the measurement was 6.5 cm. and below. At the moment I cannot explain this apparent downward trend, unless these measurements were found only in platypelloid pelves.

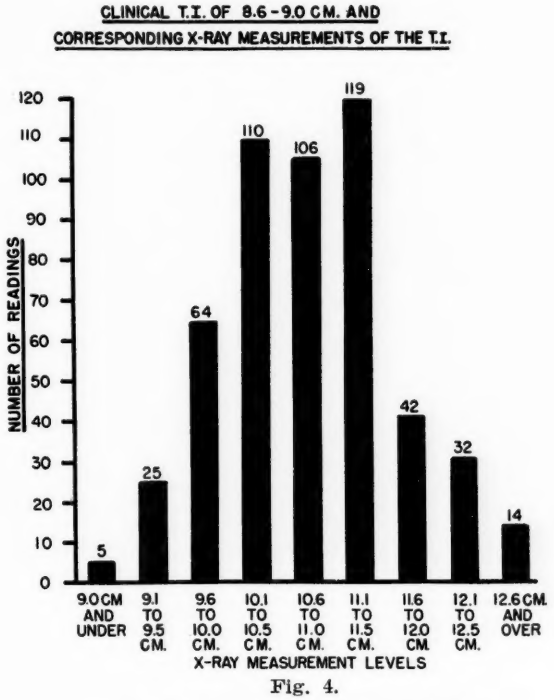

Fig. 4.

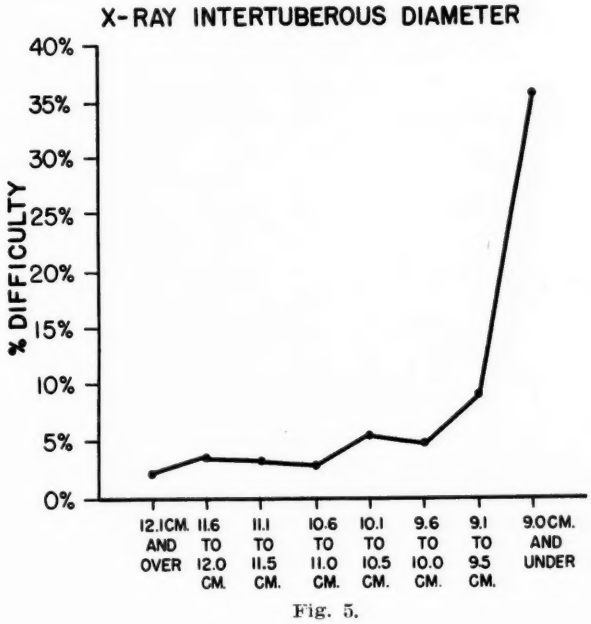

Fig. 5.

When the sums of the intertuberous and posterior sagittal diameters were examined, the curve shows very little advantage over the clinical intertuberous diameter when used by itself. (Table VI and Fig. 7.) Actually one cannot

expect to take two comparatively unsatisfactory diameters for prognosis, add them, and expect to get a more satisfactory curve. Actually the curve should be more unsatisfactory. Since the criteria recommended by McSweeney, Hanson, Bull, Daniels, McCormick, Biddle, Ragan, Mengert, etc., are variations of the intertuberous and posterior sagittal diameters of the outlet, one would expect that any examination of these various recommended yardsticks would yield results similar to those which have been found in the material just presented. Therefore, it did not seem necessary to explore further the possibilities of the intertuberous and posterior sagittal diameters from a prognostic viewpoint.

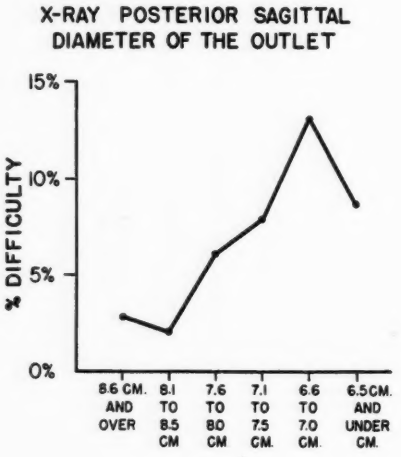

Fig. 6.

TABLE V. X-RAY POSTERIOR SAGITTAL DIAMETER OF THE OUTLET

MEASUREMENT	EASY DELIVERIES	DIFFICULT DELIVERIES	TOTAL DELIVERIES	PERCENTAGE OF DIFFICULTY
6.5 cm. and under	21	2	23	8.7
6.6-7.0 cm.	59	9	68	13.2
7.1-7.5 cm.	130	11	141	7.8
7.6-8.0 cm.	251	16	267	6.0
8.1-8.5 cm.	320	7	327	2.2
8.6 cm. and over	797	24	821	2.9
Total	1,578	69	1,647	

TABLE VI. THOMS' SUM

X-RAY MEASUREMENTS THOMS' SUM	NUMBER OF PATIENTS			
	EASY DELIVERIES	DIFFICULT DELIVERIES	TOTAL DELIVERIES	PERCENTAGE OF DIFFICULTY
16.5 cm. and under	14	5	19	26.3
16.6-17.0 cm.	27	3	30	10.0
17.1-17.5 cm.	64	8	72	11.2
17.6-18.0 cm.	96	6	102	5.9
18.1-18.5 cm.	135	13	148	8.8
18.6-19.0 cm.	190	16	206	7.8
19.1-19.5 cm.	282	11	293	3.8
19.6-20.0 cm.	211	6	217	2.8
20.1 cm. and over	471	15	486	3.1
Total	1,490	83	1,573	

The Anteroposterior of the Outlet

It is unfortunate that in collecting the material under study, the error was made of not recording the clinical anteroposterior diameter of the outlet. However, since there has been so little accuracy in clinical measurements of the pelvis as checked by x-ray in this material and in other material previously presented,[38] it is not necessarily a disastrous error. At any rate the clinical anteroposterior of the outlet cannot at this time be discussed.

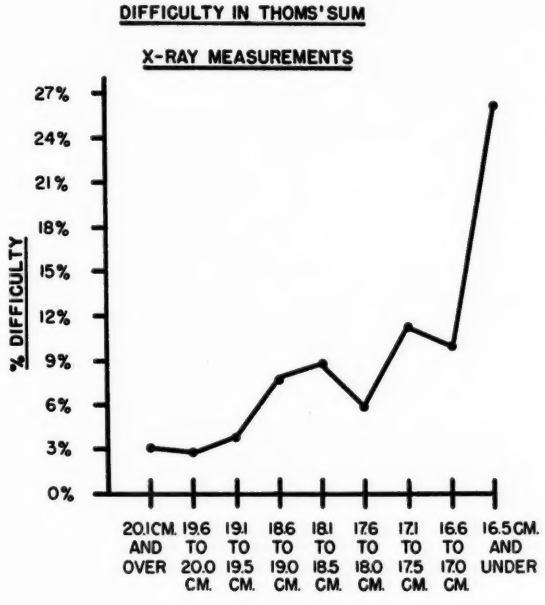

Fig. 7.

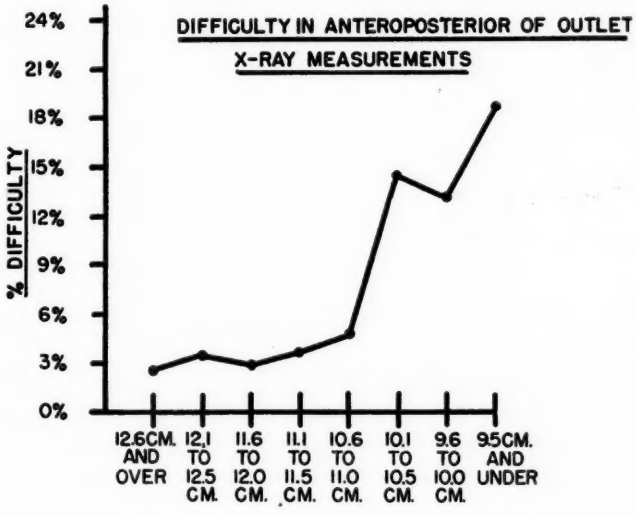

Fig. 8.

X-ray measurements of the anteroposterior diameter of the outlet on 1,575 patients, however, can be analyzed, and Table VII and Fig. 8 demonstrate

these results. It is interesting that above 10.5 cm. the expected difficulty remains about the same at any level, while below 10.5 cm. there is a definite increase in the amount of difficulty to be expected. This apparent increase is real since, first, it consists of 159 patients and, second, it is statistically valid. We are not incriminating the 10.5 cm. level as one which should be considered borderline and are not thinking of recommending that other methods than vaginal delivery be used when the diameter by x-ray is less than that. In 16 patients in which this diameter was less than 9.5 cm. only 3 had difficult vaginal deliveries and all 3 of those infants were born in excellent condition. It does suggest, however, that from a prognostic viewpoint the anteroposterior measurement of the outlet supersedes the reliability of either the intertuberous, the posterior sagittal, or their sum in prognosis.

TABLE VII. ANTEROPOSTERIOR OF OUTLET

X-RAY MEASUREMENTS* A.P.O.	NUMBER OF PATIENTS			
	EASY DELIVERIES	DIFFICULT DELIVERIES	TOTAL DELIVERIES	PERCENTAGE OF DIFFICULTY
9.5 cm. and under	13	3	16	18.7
9.6-10.0 cm.	40	6	46	13.0
10.1-10.5 cm.	83	14	97	14.4
10.6-11.0 cm.	227	11	238	4.6
11.1-11.5 cm.	278	10	288	3.6
11.6-12.0 cm.	309	9	318	2.9
12.1-12.5 cm.	226	8	234	3.4
12.6 cm. and over	329	9	338	2.6
Total	1,505	70	1,575	

*The difference between levels 10.1-10.5 cm. and 10.6-11.0 cm. is statistically significant. P = 99.8.

Can the Midplane and Outlet Be Disassociated Clinically?

It is to be recalled that so far in this analysis all patients in whom midforceps by our definition had been used have been deleted. Would the addition of midforceps delivery change the general pattern of the curves of the clinical intertuberous diameter, the clinical posterior sagittal and sum, or the x-ray intertuberous, x-ray posterior sagittal, and their sum? Table VIII and Fig. 9 show what happens when this is done with the clinical intertuberous. It may be noted that there is no essential change in the pattern of the curve. This has held true not only for the clinical intertuberous, but also for the previously

TABLE VIII. CLINICAL INTERTUBEROUS DIAMETER, LOW AND MIDFORCEPS DELIVERIES

MEASUREMENT	EASY DELIVERIES	DIFFICULT DELIVERIES	TOTAL DELIVERIES	PERCENTAGE OF DIFFICULTY
7.0 cm. and under	20	6	26	23.1
7.1-7.5 cm.	48	8	56	14.3
7.6-8.0 cm.	134	10	144	7.0
8.1-8.5 cm.	204	26	230	11.3
8.6-9.0 cm.	317	29	346	8.4
9.1-9.5 cm.	292	22	314	7.0
9.6-10.1 cm.	286	25	311	8.0
10.1-10.5 cm.	111	4	115	3.5
10.6 cm. and over	117	8	125	6.4
Total	1,529	138	1,667	

mentioned diameters and sums, and for the sake of brevity the other curves will be omitted. This suggests that when there is outlet contraction, there will generally be an accompanying midplane contraction.

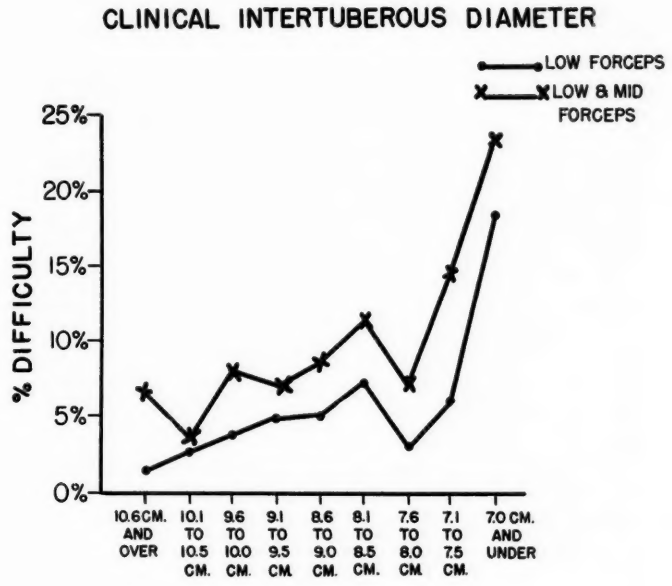

Fig. 9.

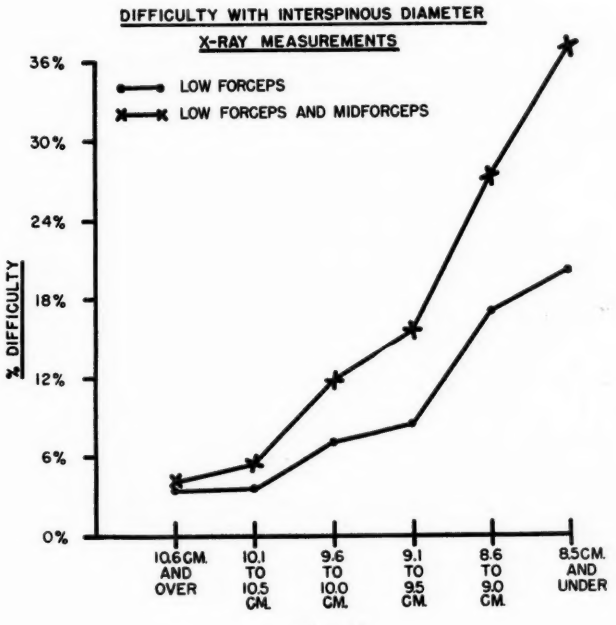

Fig. 10.

To test this hypothesis further, the interspinous diameter of the midplane was examined using, first, patients with sections for outlet contraction,

spontaneous deliveries, and low-forceps deliveries, and, second, this same group with midforceps deliveries added. Table IX and Fig. 10 demonstrate that, first, the interspinous diameter of the midplane is a better yardstick than the intertuberous and posterior sagittal with a suggestive border line of 9 cm. and, second, since the general pattern of the curve does not change when midforceps deliveries are added, therefore, from a prognostic viewpoint it is difficult to separate the midplane from the outlet.

TABLE IX. INTERSPINOUS DIAMETER

X-RAY MEASUREMENTS* I.S.	NUMBER OF PATIENTS			
	EASY DELIVERIES	DIFFICULT DELIVERIES	TOTAL DELIVERIES	PERCENTAGE OF DIFFICULTY
8.5 cm. and under	12	3	15	20.0
8.6-9.0 cm.	49	10	59	16.9
9.1-9.5 cm.	154	14	168	8.3
9.6-10.0 cm.	330	25	355	7.0
10.1-10.5 cm.	385	14	399	3.5
10.6 cm. and over	579	20	599	3.3
Total	1,509	86	1,595	

*The difference between 9.0 cm. and under and 9.1-10.0 cm. is statistically significant with the P = 99.6.

Comment

Is there any valid reason why the statistical evidence which has been presented should be true? The outlet as a unit of the pelvis has been considered as a plane in the past, but actually it is a solid in space bounded by the anterior triangle, the posterior triangle, and the anteroposterior diameter of the outlet (Fig. 11). By the time the biparietal diameter of the fetal head has reached the intertuberous diameter the suboccipitobregmatic diameter of the fetal head has already passed the anteroposterior diameter of the outlet (Fig. 12). This sort of mechanism is not true at the inlet or at the midplane of the pelvis. At the inlet, for example, the depth is usually no more than 1 or 1½ cm. while at the midplane, depending on the definition of the anteroposterior of the midplane, the depth of the midplane is either 0 cm. or 1 to 1.5 cm. (Fig. 11). From a practical viewpoint, the inlet and midplane can be considered as planes, while the outlet must be considered as a solid. During the second stage of labor, the biparietal diameter is passing the ischial spines at about the same time that the suboccipitobregmatic is passing the anteroposterior of the outlet (Fig. 13). The biparietal, depending on the width of the intertuberous and on the acuteness of the subpubic angle, next passes through the intertuberous or inferior to it. While the biparietal diameter of the fetal head is passing this area, the suboccipitofrontal diameter of the fetal head has already passed the anteroposterior of the outlet. All of us have experienced in vaginal deliveries resistance to extraction until the brow of the infant has passed the end of the sacrum. Part of this difficulty is due to the fact that with forceps deliveries, as has been noted by Hanson,[37] there is some extension of the fetal head, and when better flexion in forceps delivery is maintained, either by traction with the forceps posteriorly or by the application of fundal pressure, this resistance of the brow is overcome.

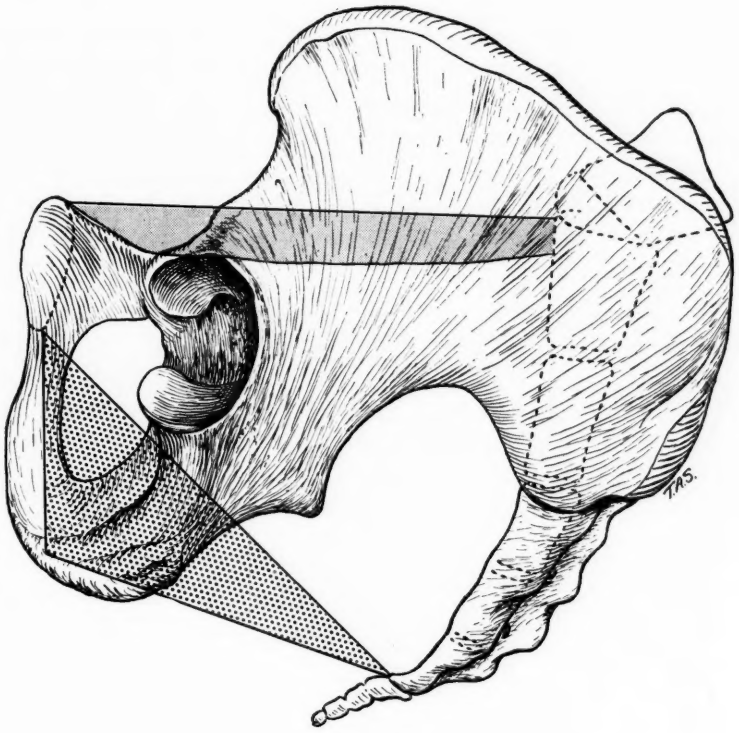

Fig. 11.

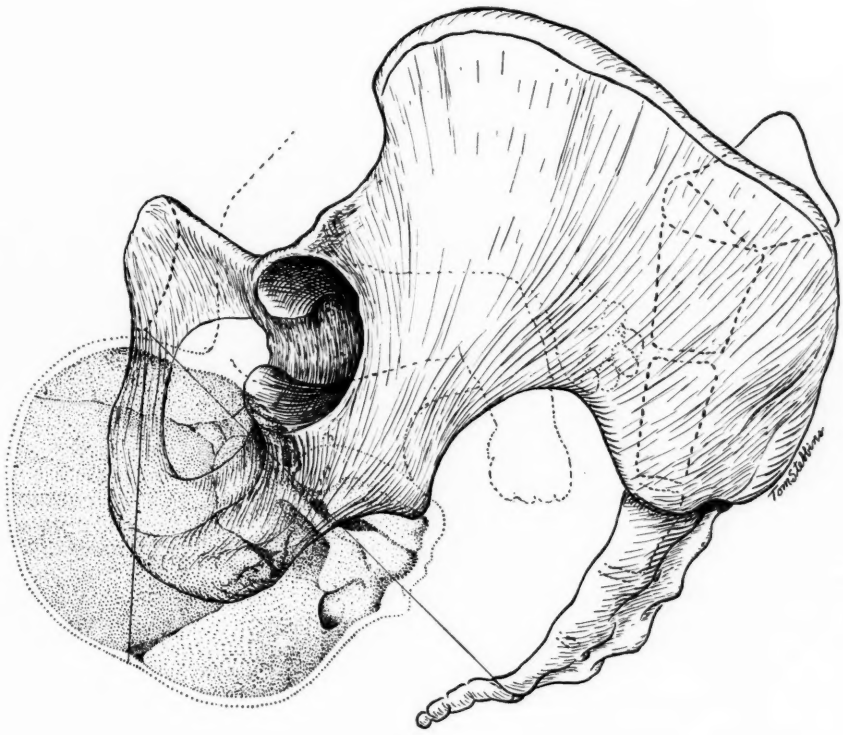

Fig. 12.

The small plane of the pelvis, the midplane, on the other hand, is from a practical viewpoint a plane without depth, so that in a well-flexed head, when the biparietal diameter is passing at or near the ischial spines, the suboccipitobregmatic is at or near the anteroposterior of the outlet. From this plane inferiorly, regardless of what the actual measurements may be, one is at no point bringing the suboccipitobregmatic-biparietal plane of the fetal head through the smallest diameters of the outlet. It may be this situation which explains the difficulty of separating the midplane and outlet in practical obstetrics.

Obviously, in many difficult forceps deliveries, other factors are playing a role. A frequent one is soft-tissue resistance. We have seen, on a number of occasions, patients with good second-stage labor fail to make proper descent to the perineum only to find that, when saddle anesthesia has been given, the head descends easily, because the soft-tissue resistance has been eliminated.

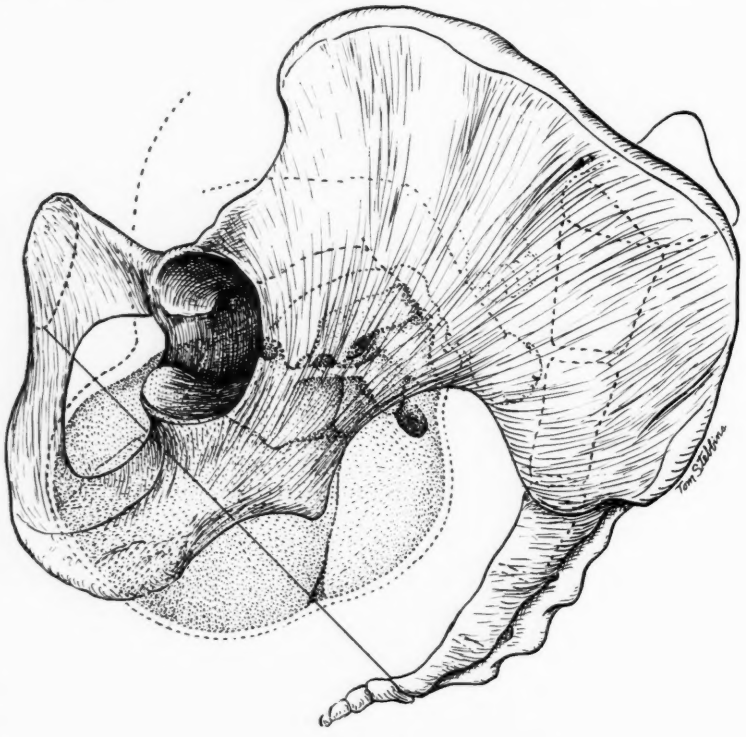

Fig. 13.

A second factor may be insufficient expulsive power due either to inadequate uterine contractions or to failure of use of the abdominal-wall musculature to accomplish rotation or descent to the perineal floor. Frequently we have been surprised to find rotation easily accomplished and the delivery consummated with minimal traction, when it was not expected. Another peculiarity we have encountered in outlet delivery is the refusal of the transverse occiput to rotate spontaneously, manually, or with forceps without excessive effort. In many of these instances, the occiput transverse positions may be delivered as such or in the oblique diameter with the brow using the area between the end of the sacrum and the ischial spines on one side or the other.

Another not uncommon occurrence is a head with unrecognized molding which has descended to the perineum with bulging. In these instances the largest diameter of the head may still be well above the midplane and we have on record one extreme case in which the biparietal of the fetal head was still above the transverse diameter of the inlet.

Another concept to be considered is in some variance with the usually accepted ideas of the head traversing the various planes of the pelvis. Let us look at the pelvic cavity as a whole, remembering that the fetal head is a comparatively large solid. We have seen on many occasions fetal heads at 1 or 2 cm. below the spines in pelves with large midplane measurements, in which there has been difficult extraction. Even though the presenting part has been well below the spines, the brow of the infant has had difficulty surmounting the inlet. Obviously, in a great many instances this has been in a poorly flexed head. We have also found by statistical analysis that in pelves in which Mengert's areas at the midplane have been above the 85 per cent borderline level, the amount of difficulty with vaginal delivery is twice as great when the inlet

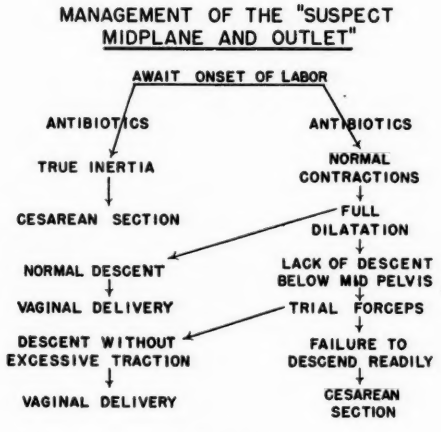

Fig. 14.

is below Mengert's 85 per cent borderline area.[39] So in many instances when we thought we were having difficult vaginal delivery due to the midplane, the inlet was actually the basis of difficulty. The same correlation can be made between the outlet and midplane, although from a statistical viewpoint it is much more difficult to assess unless we are able to have lateral roentgenograms of all these patients at the time of delivery and determine the relation between the suboccipitobregmatic-biparietal plane of the fetal head and the ischial spines.

Management

Because of our statistical data and our reasoning with the various factors involved, we are forced to relieve the intertuberous and posterior sagittal diameters of the outlet of the responsibility for prognosis and depend upon the interspinous and anteroposterior diameters. In addition we are forced to believe that the midplane and outlet should be considered as one from a practical

viewpoint and that in most instances when we have thought the outlet to be at fault, it actually has been the midplane. Because of the large number of times we have experienced ease of delivery when we had contemplated difficulty and because of the few times when we expected ease of delivery and encountered difficult extraction, we have assumed the method of management of patients with a suspect outlet or midplane outlined in Fig. 14.

When there is an abnormal presentation, such as a breech, the decision must be made before labor, and in making that decision the general pelvic contour, pelvic measurements, and general fetal size must be taken into consideration. In vertex presentations, we await the spontaneous onset of labor. Antibiotics with a wide range are started, since at that moment we do not know how long the labor will last, nor whether the patient will be delivered abdominally. If true inertia develops, and there must be dilatation and effacement of the cervix for that diagnosis to be made, cesarean section is the procedure of choice. If normal contractions ensue, full dilatation of the cervix may be expected within a reasonable time. If there is normal descent in the second stage of labor, a spontaneous or easy low-forceps delivery may be expected. If the presenting part fails to descend during the second stage of labor to bulging of the perineum, a trial of forceps delivery is made. If there is lack of descent with gentle traction and vis a tergo, we do not hesitate then to deliver the patient abdominally through a laparotrachelotomy incision or via the extraperitoneal route, if desired.

TABLE X. TRIAL FORCEPS DATA

	GROUP I 7/1/47—8/1/51	GROUP II SINCE 8/1/51
Total cases	292	133
Easy vaginal deliveries	177	79
Difficult vaginal deliveries	107	49
Cesarean section without forceps	7	0
Cesarean section with forceps	1	5
Section rate	2.7%	3.8%
Pertinent deaths	13	0
Percentage of deaths	4.5%	0.0%
Pertinent injury in live infants	5	4
Pertinent deaths and injuries	18	4
Percentage	6.2%	3.0%
Causes injury and death		
Intracranial hemorrhage	9	2
Shoulder dystocia	6	2
Second-stage anoxia	3	0

If this type of management is to be acceptable we must deliver as many infants vaginally as possible, but without infant injury, and that includes those infants who are discharged alive from the hospital. The following were our results before this line of management was followed, and we felt obligated to vaginal delivery once the forceps blades were applied. These cases must of necessity include all patients regardless of fetal weight (Table X). From July 1, 1947, to Aug. 1, 1951, we had 1,189 vertex vaginal deliveries in which x-ray pelvimetry was obtained. Of those, forceps were indicated in 292 cases, of which 177 were easy forceps deliveries and 107 were difficult. There were 7

cesarean sections done without attempts at vaginal delivery and 1 cesarean section after forceps failure. The fetal death rate was 4.5 per cent with an additional 5 infants injured. We have included shoulder dystocia because in each of these there was excessive traction necessary on the forceps to deliver the head. After delivery of the head, the shoulder dystocia was recognized.

In the group of patients in whom we did not feel obligated to vaginal delivery after application of the forceps, there were 133 patients in 810 vertex vaginal deliveries. Seventy-nine delivered easily vaginally and 49 delivered with difficulty vaginally. There were 5 forceps failures followed by cesarean section. There were no fetal deaths and 4 infants were affected, all of whom were discharged alive. Two had intracranial hemorrhage and 2 had shoulder dystocia.

In our first paper[40] on this subject we did not include the easy low-forceps deliveries which we encountered when forceps were indicated, and used only the midforceps and difficult low-forceps. This, we feel, was in error and we are attempting to correct this mistake at this time.

We are not convinced that this is the ultimate answer to this problem because: (1) some inexperienced operators will, without a doubt, use too much traction; (2) there must be some infants who receive intracranial damage before attempts at delivery due to excessively potent uterine contractions and variations in each infant's ability to mold without intracranial damage; and (3) the diagnosis of shoulder dystocia in these difficult vertex deliveries before the head is delivered is going to be extremely difficult, although we should reevaluate fetal size when the pelvis does not seem too contracted and the forceps traction is not easy. However, we are sufficiently impressed with our reduction in fetal mortality with this group of patients at this time to continue with the trial forceps in practice.

Conclusions

1. The anteroposterior diameter of the outlet is a better prognostic tool in outlet delivery than the intertuberous, posterior sagittal, and their sum.

2. The outlet and midplane should be considered as one in management of suspect pelves.

3. The interspinous diameter of the midplane is useful in prognosis of outlet contraction.

References

1. Williams, J. W.: Surg., Gynec. & Obst. **8**: 619, 1909.
2. du Coudray: Abrege de l'Art des accouchements, 1769, Nouv. Ed. Saintes. (Quoted by Williams.[1])
3. Busch: Ztschr. f. Geburtsh., vol. 168, 1937. (Quoted by Williams.[1])
4. Busch: Die theoretische und practische Geburtskinde, Berlin, 1838. (Quoted by Williams.[1])
5. Kilian: Die Geburtslehre von Seiten der Wissenschaft und Kunst dargestellt, Frankfurt, 1839. (Quoted by Williams.[1])
6. Ritgen: Monatschr. f. Geburtsh. **10**: 401, 1857.
7. Dedolph: Ueber ein im Ausgang verengtes Becken, 1869, D. I. Marburg. (Quoted by Williams.[1])
8. Briesky: Med. Jahr. **30**: 1, 1870.
9. Champneys: (Quoted by Nicholson.[27])
10. Klien, R.: Monatschr. f. Geburtsh. u. Gynäk. **2**: 165, 1895.

11. Klien, R.: Samml. klin. Vortr. 169, 1896.
12. Klien, R.: Zentralbl. f. Gynäk. **21**: 131, 1897.
13. Williams, J. W.: Am. J. Obst. **64**: 106, 1911.
14. Williams, J. W.: Obstetrics, ed. 6, New York, 1930, D. Appleton and Company.
15. Thoms, H.: Am. J. Obst. **72**: 121, 1915.
16. McSweeney, D. J.: AM. J. OBST. & GYNEC. **63**: 765, 1952.
17. Hanson, S.: AM. J. OBST. & GYNEC. **35**: 228, 1938.
18. Bull, H. C. H.: J. Obst. & Gynaec. Brit. Emp. **58**: 22, 1951.
19. Schuman, W.: AM. J. OBST. & GYNEC. **28**: 497, 1934.
20. Daniels, C. D.: Am. J. Obst. **74**: 238, 1916.
21. McCormick, C. O.: AM. J. OBST. & GYNEC. **11**: 794, 1926.
22. Moir, C.: Edinburgh M. J. **48**: 361, 1941.
23. Williams, E. R., and Phillips, L. G.: J. Obst. & Gynaec. Brit. Emp. **53**: 125, 1946.
24. Morris, W. I. C.: Lancet **139**: July 24, 1948.
25. Biddle, A. G.: Am. J. Obst. **65**: 987, 1912.
26. McSweeney, D. J., and Moloney, A. M.: AM. J. OBST. & GYNEC. **46**: 102, 1943.
27. Nicholson, W. R., and Tauber, R.: AM. J. OBST. & GYNEC. **51**: 538, 1946.
28. Ragan, C. J., Levy, W. E., and King, E. L.: AM. J. OBST. & GYNEC. **41**: 79, 1941.
29. Pieri, R. J.: Surg., Gynec. & Obst. **59**: 891, 1934.
30. Williamson, M.: Am. J. Obst. **78**: 528, 1918.
31. Cummings, H. H.: J. Michigan M. Soc. **10**: 625, 1911.
32. Stude, W. C.: Illinois M. J. **66**: 171, 1934.
33. Mengert, W. F., and Eller, W. C.: AM. J. OBST. & GYNEC. **52**: 1032, 1946.
34. Moir, C.: J. Obst. & Gynaec. Brit. Emp. **56**: 189, 1949.
35. Allen, E. P.: Brit. J. Radiol. **16**: 279, 1943.
36. Allen, E. P.: Brit. J. Radiol. **20**: 164, 1947.
37. Hanson, S.: AM. J. OBST. & GYNEC. **29**: 571, 1935.
38. Kaltreider, D. F.: AM. J. OBST. & GYNEC. **61**: 1075, 1951.
39. Kaltreider, D. F.: AM. J. OBST. & GYNEC. **63**: 392, 1952.
40. Douglass, L. H., and Kaltreider, D. F.: AM. J. OBST. & GYNEC. **65**: 889, 1953.

THE RELIEF OF THE PAINS OF LABOR BY THE CONTINUOUS INTRAVENOUS DRIP OF MEPERIDINE* AND SCOPOLAMINE

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WOMEN, for countless ages, have sought relief from the pangs of labor. Indeed, the proponents of natural childbirth do not hesitate to administer pain-relieving drugs. Anyone who has suffered from colic, either renal, vesical, uterine, etc., knows that the suffering is real and not a figment of the imagination.

Our[1] experience with the continuous intravenous infusion of meperidine and scopolamine for the relief of the parturient woman has been highly gratifying.

There are numerous reports on the effects of the intravenous administration of various drugs on women in labor. Brown and associates[2] described the intravenous use of meperidine and scopolamine as does Cowden,[3] but both gave it as a slowly injected single dose and not as a continuous drip. Jeffcoate[4] employed the continuous intravenous drip of meperidine and scopolamine in abnormal uterine action, and both he and Theobald[5] are very enthusiastic about its beneficial action.

The adage that where there are many remedies for a condition the ideal remedy has yet to be discovered holds true in the case of labor pains. However, a study of the pharmacology of the drugs we employ and the experience we have gained in observing their effects convinces us that the continuous intravenous drip of meperidine and scopolamine comes close to the ideal.

Meperidine[6, 7] is a synthetic compound, which when given in doses of 100 mg. either orally or parenterally has an analgesic action which lies midway between morphine and codeine. It is spasmolytic, having an atropine-like action. Its effects are both central and peripheral; while acting to relax spastic musculature it simultaneously produces central analgesia. It blocks parasympathetic innervation and also acts as a vasodilator, causing some lowering of blood pressure. It does not depress the medulla, and cough and respiration are not affected. Severe respiratory depression is rarely seen. Cohen[8] cites a case where a patient took 1,250 mg. with suicidal intent and he developed only mild symptoms and recovered without sequelae. Meperidine has been shown to be less constipating than morphine and less likely to cause postoperative ileus and urinary retention.

*Demerol is the trade name for meperidine.

The side effects of meperidine are dryness of the mouth, excessive perspiration, and dizziness.

Meperidine is almost completely destroyed by the liver, and Apgar[9] found that it crosses the human placenta.

King and co-workers[10] found that tilting the patient to a 60 degree "head up" position after the administration of 100 to 150 mg. of meperidine intravenously increases the incidence of circulatory collapse, and that the incidence is significantly less after meperidine than after morphine. We have had no occasion to tilt our patients, and we have had no cases of circulatory collapse.

Scopolamine[11] is only a weak vagal depressor; it combats respiratory depression and produces both psychic sedation and amnesia. It has the disadvantage of being somewhat irregular in its action and may at times produce excitement and delirium.

Materials and Methods

One hundred twenty-one patients, both ward and private, were chosen at random. Their ages ranged from 16 to 46 (Table I). There were 44 nulliparas and 77 multiparas (Table II).

TABLE I. AGE OF PATIENTS

UNDER 20	20-24	25-29	30-34	35-39	OVER 40
10	33	43	23	11	1

TABLE II. PARITY

PARA 0	PARA I	PARA II	PARA III	ABOVE III
44	47	19	8	3

Intravenous solutions were prepared by dissolving .002 Gm. of meperidine and .0006 Gm. of scopolamine in 500 ml. of 5 per cent glucose in water. Only 6 patients received sedatives (barbiturates) prior to the infusion.

Infusions were started when the patient was considered to be in active labor (Table III). In nulliparas the infusions were begun when the pains varied in intensity either objectively or subjectively from moderate to strong. In most cases it was not necessary to begin infusing until the contractions occurred at intervals of from 4 to 6 minutes. In multiparas, the infusions were commenced when the pains were mild to moderate and the intervals 5 to 10 minutes. In patients who were unusually tense and anxious, both nulliparas and multiparas, the infusions were started sooner than in the better poised woman.

TABLE III. DILATATION OF CERVIX AT START OF INFUSION

	2 CM.	4 CM.	6 CM.	8 CM.	FULLY DILATED
Primiparas	4	19	12	6	3
Multiparas	12	30	27	6	2

Patients were closely observed by the staff until the desired analgesia was obtained. The infusion was then slowed to the maintenance rate, and from then on, except in occasional instances, could be adequately followed by the nursing staff as very little further regulation of the infusion was required.

Seventeen patients in this series were admitted in the latter stages of labor. Five patients who were approaching the end of the first stage and who were being infused with meperidine and scopolamine developed uterine inertia and were given small divided doses of Pitocin intramuscularly.

Labor was induced in 3 patients by the continuous intravenous infusion of Pitocin and when labor was established intravenous meperidine and scopolamine were simultaneously administered, employing a separate bottle and vein so that the rate of flow of each solution could be individually controlled.

The solution was introduced intravenously, employing a No. 20 gauge needle preferably in one of the dorsal veins of the hand. This permitted the patient freedom of motion with little likelihood of displacing the needle. Two hundred fifty milliliters of the solution was administered as rapidly as possible. Most patients at this time were drowsy and quite relaxed. The uterine contractions continued and were deemed in the vast majority of cases to be as forceful as before the infusion, but the patients' reactions to these contractions were much less intense.

It is essential if success is to be achieved by this method that patients be treated individually. Some patients will require a higher maintenance level than the average and vice versa.

After the initial calm and relaxation are obtained, the infusion is then slowed to 10 to 40 drops per minute and continued until delivery has taken place. The rate of infusion is determined by the patient's reaction to the uterine contractions. Should the first 500 ml. of solution be used up before the patient be delivered, a similar 500 ml. solution is immediately connected to the intravenous system.

Results

The great majority of patients obtained adequate pain relief. In 72 per cent of the cases, the result was considered excellent. Table IV gives the results in detail. These were evaluated both objectively and subjectively and by interviews with the patients from 12 to 24 hours after delivery.

The amnestic effects were likewise very satisfactory. Despite the fact that 17 patients are included in this table who were given the infusion late in labor, 70 per cent of the total stated that they remembered nothing of the delivery (Table IV). Had these patients been admitted to the hospital earlier, the percentage of patients with complete amnesia would undoubtedly have been higher. This last group enjoyed satisfactory analgesia.

To test the importance of the synergism of the two drugs, scopolamine was omitted and meperidine alone administered in a few cases. These patients did not obtain the same degree of relaxation, analgesia, and amnesia as did the patients who received both drugs.

The average duration of labor in the nulliparas was 11.4 hours and in the multiparas 6 hours (Table V).

The average duration of the infusion in nulliparas was 4.1 hours and 1.2 hours in multiparas. Since most patients were infused when active labor was in progress, it can be seen that the duration of their active stages was shortened when compared with the accepted averages.

The average amount of solution infusion was 640 ml. in nulliparas and 475 ml. in multiparas. Twelve patients received 1,000 ml. and no ill effects were noted either in mother or infant.

TABLE IV. RESULT OF INFUSION

	ANALGESIA*				AMNESIA†			
	E	G	F	P	E	G	F	P
Primiparas	33	9	2	0	31	8	4	1
Multiparas	54	19	3	1	54	15	5	3

Analgesia:
E—No evidence of pain.
G—Marked relief from pain.
F—Some relief from pain.
P—Slight or no relief from pain.

†*Amnesia:*
E—Remembered nothing.
G—Remembered isolated instances of persons.
F—Hazy memory of labor.
P—Remembered labor.

TABLE V. AVERAGE DURATION OF LABOR AND AMOUNT OF INFUSION GIVEN

	AVERAGE DURATION OF LABOR PRIOR TO INFUSION	AVERAGE TOTAL DURATION OF LABOR	AVERAGE DURATION OF INFUSION	AVERAGE AMOUNT OF INFUSION GIVEN
Primiparas	7 hours	11.4 hours	4.1 hours	640 c.c.
Multiparas	4.8 hours	6.0 hours	1.2 hours	475 c.c.

Seventy-four per cent of the patients had no side effects (Table VI). Excitement was observed in 8 patients, and this was especially marked in patients in whom the infusion had been interrupted close to the time of delivery. In some of these patients, the sudden contrast between the absence of pain and its sudden occurrence after the accidental or intentional interruption of the infusion might explain the excitement.

Slowing of labor was a minor problem having been observed in only 2 patients.

TABLE VI. SIDE EFFECTS OF INFUSION

NONE	NAUSEA	VOMITING	SLOWING OF LABOR	EXCITE-MENT	PROFUSE SWEATING	DIZZINESS	TACHY-CARDIA
90	12	7	2	8	2	15	2

Sixty-three per cent of the patients delivered spontaneously (Table VII). There were 3 assisted breech deliveries. These patients responded very well to verbal instructions when the breech presented at the vulva.

TABLE VII. METHOD OF DELIVERY

	SPONTANEOUS	MIDFORCEPS INCLUDING ROTATIONS	LOW OR OUTLET FORCEPS	BREECH DELIVERY
Primiparas	17	2	24	1
Multiparas	60	2	13	2

Twenty per cent of the patients required no supplemental anesthesia. In 8 per cent, pudendal block only was employed (Table VIII). The amount of supplementary anesthesia was much less than in comparable cases where other methods of sedation were employed.

The effect on the infants at birth was very gratifying. Eighty-eight per cent cried instantly and vigorously and had good color (Table IX). Five per cent (6 infants) required resuscitation, and of these one was born with hydrocephalus.

TABLE VIII. SUPPLEMENTARY ANESTHESIA

	NONE	GAS OXYGEN	GAS OXYGEN ETHER	PUDENDAL BLOCK	PUDENDAL GAS OXYGEN	OPEN ETHER
Primiparas	7	8	18	6	5	0
Multiparas	18	23	29	4	2	1

TABLE IX. CONDITION OF BABIES AT BIRTH

COLOR AND CRY GOOD	MILD CYANOSIS	NEEDED RESUSCITATION
108	8	6

The size of the uterus was deceptive in 3 cases, and the infants born weighed between 4½ and 5 pounds. These babies cried lustily at birth, and there were no complications. Three infants were born to mothers suffering from toxemia. Three Rh-positive infants were born to Rh-negative mothers. There was one set of twins. All of these babies had uncomplicated courses.

Ninety-seven per cent of the infants were apparently normal on discharge (Table X). There was one case of hydrocephalus, and this infant on discharge was otherwise in apparently good condition.

TABLE X. CONDITION OF BABIES ON DISCHARGE

APPARENTLY NORMAL	STILLBORN	NEONATAL DEATHS	CONGENITAL ABNORMALITIES
119	0	1	2

There was one neonatal death in which autopsy revealed congenital heart disease.

None of the mothers in this series required postpartum catheterization. There were no maternal deaths, and according to the accepted standards there was no maternal morbidity.

Among the patients infused, there were cases of secondary anemia, decompensated rheumatic heart disease, healed pulmonary tuberculosis, multiple furunculosis, previous colon resection for carcinoma, previous shock therapy for psychosis, toxemia of pregnancy, premature separation of the placenta, and retained succenturiate placental lobe. This latter patient suffered a postpartum hemorrhage.

Comments

From the study of our series, we are satisfied that the combination of meperidine and scopolamine infused intravenously by the continuous drip method is a safe and effective means of securing satisfactory analgesia and amnesia in labor.

As concerns maternal and fetal mortality and morbidity, the results in this series are comparable to those observed in patients who received no medications.

The patients were extremely grateful for the relief accorded them. Many of them were so favorably impressed that they expressed the desire to be delivered in the same manner in future pregnancies.

This technique requires no special equipment other than that present in the average delivery suite. The nursing problem is not unduly complex.

In our opinion, labor is appreciably shortened, and in most instances the patients are easily controlled.

We feel that the combination of meperidine and scopolamine has a synergistic effect, and that the omission of either drug or the diminution of the amounts will yield a less satisfactory result.

It is our experience that the best results are obtained by an initial rapid infusion followed by adequate maintenance. It is important that the infusion be continued during the actual delivery even in the cases where supplementary anesthesia is required. We have found that by so doing the restlessness so often present in the second stage of labor is greatly eliminated, and should inhalation anesthesia be required, its induction is facilitated and the amount of anesthetic solution needed is greatly reduced. An appreciable number of patients can be delivered without the employment of any anesthesia. When indicated, we have found that this method yields excellent results combined with the technique of pudendal block or local infiltration anesthesia.

We have never found it necessary to administer more than 400 mg. of meperidine. However, we would not hesitate to continue the infusions beyond this amount since Jeffcoate reports giving 800 mg. by continuous intravenous infusion within 24 hours without untoward results.

Because of the rapidity of its action we find this method very valuable in patients who enter the hospital in the terminal stages of labor.

Summary

1. One hundred twenty-one patients in labor were given dilute solutions of meperidine and scopolamine by a continuous intravenous drip.

2. There were 44 nulliparas and 77 multiparas in this series.

3. The patients were unselected and included cases of twins, breech presentations, toxemias of pregnancy, rheumatic heart disease, and Rh-negative mothers.

4. Synergism of meperidine and scopolamine was demonstrated.

5. A high percentage of analgesia and total amnesia was obtained.

6. The active stage of labor was appreciably shortened.

7. Fetal complications were not increased.

8. Except for a postpartum hemorrhage in a patient who had a succenturiate placental lobe, there were no postpartum maternal complications.

9. There were no maternal deaths and no morbidity.

Conclusion

Dilute solutions of meperidine and scopolamine when administered intravenously by a continuous drip afford a safe and efficient method of relieving the pains of labor and of securing of amnesia.

References

1. Rosenfeld, S. S., Lapan, B., and Weinstein, M. S.: Bull. New York Acad. Med. **28**: 545, 1952.
2. Brown, J. M., Volpitto, P. P., and Torpin, R.: Anesthesiology **10**: 15, 1949.
3. Cowden, A. M.: J. M. A. Alabama **21**: 53, 1951.
4. Jeffcoate, T. N. A.: J. Obst. & Gynaec. Brit. Emp. **59**: 658, 1952.
5. Theobald, G. W.: J. Obst. & Gynaec. Brit. Emp. **59**: 659, 1952.
6. Beckman, H.: Pharmacology in Clinical Practice, Philadelphia, 1952, W. B. Saunders Company, p. 473.
7. Salter, W. T.: A Textbook of Pharmacology, Philadelphia, 1952, W. B. Saunders Company, p. 75.
8. Cohen, A. E.: Ann. Allergy **8**: 547, 1950.
9. Apgar, V., Burns, J. J., Brodie, B. B., and Papper, E. M.: Am. J. Obst. & Gynec. **64**: 1368, 1952.
10. King, B. D., Elder, J. D., and Dripps, R. D.: Surg., Gynec. & Obst. **94**: 591, 1952.
11. Beckman, H.: Pharmacology in Clinical Practice, Philadelphia, 1952, W. B. Saunders Company, p. 73.

EXPERIENCE WITH HYDRAZINOPHTHALAZINE IN HYPERTENSIVE STATES OF PREGNANCY

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TOXEMIA and hypertension of pregnancy have been treated by various means. Sedatives, anticonvulsants, anesthetics, and many other drugs have been used with far from satisfactory results. In recent years Veratrum and its derivatives have once again become popular, and even more recently the newer antihypertensive agents have been discovered.

Gross, Druey, and Meier[1] in 1950 demonstrated that the phthalazine group of drugs when given to animals act as vasodepressors and increase the pulse rate and renal blood flow. Much has since been written concerning their use in hypertensive states. Reubi and associates[2, 3, 4] in 1949 and 1950 described increased renal blood flow observed with concomitant hypotensive response.

Grimson, Chittum, and Metcalf[5] believed the drug to be sympatholytic because in some animals it acted in a manner antagonistic to epinephrine. There is some evidence, however, that the drug acts centrally on the vasomotor center or is antagonistic to vasopressor substances.[1, 6, 7, 8] Moyer, Handley, and Huggins[9] concluded that in unanesthetized dogs renal blood flow is increased without an associated increase in glomerular filtration rate or in maximal tubular reabsorption of glucose. The increase in renal blood flow is roughly proportional to the increase in cardiac output. Epinephrine blockade could not be demonstrated following the intra-arterial use of 1-hydrazinophthalazine.

The actual site of action is unknown. The drug has been found effective in various types of hypertensive patients including those with unsuccessful sympathectomy, malignant hypertension, and neurogenic hypertension.[6, 7] The maximum effect is on the diastolic blood pressure. Only occasionally is the drug of therapeutic value when used alone in hypertensive vascular disease, but when combined with other agents it has proved effective.[10] It is relatively ineffective in renal hypertension.[6, 7] Hafkenschiel and co-workers[11] report reductions in cerebral pressure, resistance, and in the increased tone of the cerebral vessels in patients with hypertensive vascular disease after intramuscular 1-hydrazinophthalazine.

In a recent report including 17 toxemic and 15 hypertensive pregnant patients, Assali and Suyemoto[12] concluded that after one intravenous dose of 1-hydrazinophthalazine the average blood pressure reductions in the toxemic group were 26 per cent systolic, 43 per cent diastolic, with the diastolic responding first and to a greater degree. In the hypertensive group the

average decreases were 11 per cent systolic, 19 per cent diastolic. They demonstrated that renal blood flow increased, glomerular filtration rate decreased, urine volume remained constant or slightly decreased, and urine concentrations of sodium and chloride diminished or remained unchanged. Assali and associates[13, 15] conclude that although the mechanism of action of l-hydrazinophthalazine is obscure, its hemodynamic effects are different from those produced by ganglionic and adrenergic blocking agents.

Present Studies

To date Apresoline (1-hydrazinophthalazine) has been evaluated as follows in 34 pregnant patients:

A. Twenty-one patients received the drug intravenously.

B. Five patients received the drug orally or subcutaneously.

C. Eight patients received the drug intravenously *and* orally or subcutaneously.

Classification.—The patients are divided into the following classes:

A. Sixteen pre-eclamptic patients with hypertension, albuminuria or edema. Two of these were always present.

B. Five hypertensive pregnant patients (hypertension without albuminuria or edema).

C. One hypertensive patient with superimposed pre-eclampsia and previous sympathectomy (hypertensive history with additional findings of edema, albuminuria, and further rise in blood pressure).

D. Twelve patients with "hypertension in labor."

This latter group is proposed for patients who manifest the hypertensive state for the first time when in labor with no albuminuria or edema, no significant history, and whose blood pressures return to normal in the puerperium. Until now these patients have been classed at this institution as hypertensive, but it is felt that rather than classify them with inadequate data as the basis, a special group might better answer the problem pending the long-term follow-up which we feel is necessary for accurate diagnosis. For comparative purposes this group can be placed with the hypertensive patients. Retinal patterns were not considered different in toxemia as compared with hypertension.

Mode of Administration.—Twenty-nine patients who did not respond to control therapy were given the drug. Those not in labor were given at least 24 hours of bed rest and mild to heavy sedation as control therapy. Those already in labor when first seen were given several hours of control therapy prior to administration of 1-hydrazinophthalazine. Control therapy in both classes included two or more of the following drugs (usually three or more): 1 to 3 Gm. of intravenous or intramuscular magnesium sulfate, 200 to 500 mg. of intravenous Nembutal, 50 to 150 mg. of intravenous or intramuscular meperidine, 10 to 15 mg. of morphine sulfate, or 200 mg. oral phenobarbital.

Intravenous Administration.—Intravenous injection was carried out in the following manner: Apresoline, 20 to 40 mg., was given slowly over a 5 to 10 minute period. Maximal responses could usually be demonstrated 10 to 20 minutes after initiation of the injection. Two physicians were always present,

one taking blood pressures, the other administering the drug. The blood pressure was recorded at 10 to 20 second intervals during the injection and only as much of the drug as was necessary to reduce the pressure to within normal limits was used, with the emphasis being placed on the diastolic pressure. The diastolic always fell first and to the greater degree. In fact, on occasions the systolic pressure increased over the control, but then fell at least to control level and more often lower, as the actual percentile reductions listed verify. Blood pressures were recorded at 5 minute intervals following completion of the injection for a half-hour period, then every 15 minutes for the next half-hour. Thirty minute intervals, or more frequently if necessary, were then observed between pressure recordings. Pulse rate and the time of the onset of facial flush were also noted. This routine was again followed if another dose was indicated.

Results

In most instances the maximal blood pressure response was obtained prior to the 30 minute level, but this level was not always maintained. Thus, rather than record average results, using as a basis only the maximal responses, it is felt that a clearer picture of predictable response could be obtained if only those pressures existing 30 and 60 minutes following the initiation of injection are used. Average duration of action was noted between one and 6 to 8 hours. Dosage varied between 20 and 40 mg., most patients requiring 30 to 40 mg. per dose.

Based on individual doses rather than patients, some of whom received multiple doses, the following average blood pressure reductions were achieved (one hypertensive patient received eight doses without significant response):

A. Pre-eclamptic group: systolic pressure 13.7 per cent in 30 minutes, 14.4 per cent in 60 minutes; diastolic pressure 33.7 per cent in 30 minutes, 36.6 per cent in 60 minutes.

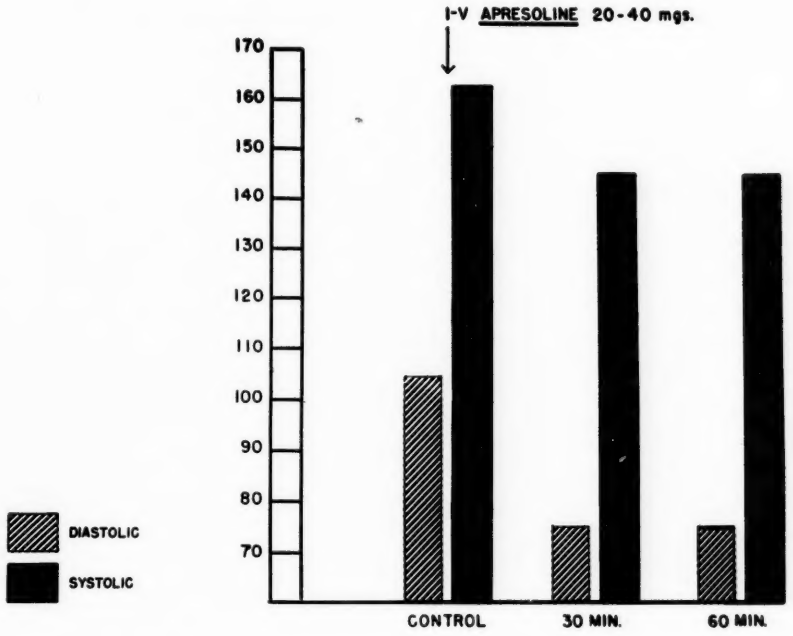
B. Hypertensive group: systolic pressure 2.4 per cent in 30 minutes, 2.9 per cent in 60 minutes; diastolic pressure 13.2 per cent in 30 minutes, 8.6 per cent in 60 minutes. It should be especially mentioned here that the eight individual doses given to the one patient who failed to respond in this group attribute a disproportionate weight to this patient as compared to the 3 having good responses and one fair (these four having five doses altogether). If this patient had only one or even two doses the percentile reductions for the entire group would be as follows: systolic reduced 9.8 per cent in 30 minutes, 13.0 per cent in 60 minutes; diastolic 22.1 per cent in 30 minutes, 22.0 per cent in 60 minutes.

C. Hypertension in labor only: systolic pressure 12.5 per cent in 30 minutes, 12.6 per cent in 60 minutes; diastolic pressure 42.3 per cent in 30 minutes, 35.4 per cent in 60 minutes.

D. Hypertension with superimposed pre-eclampsia: One patient whose systolic pressure was reduced 8.5 per cent in 30 minutes, 9.8 per cent increased in 60 minutes; diastolic reduced 52.4 per cent in 30 minutes, 14.3 per cent in 60 minutes.

A composite blood pressure graph and graphs of two typical responses to intravenous 1-hydrazinophthalazine follow (Figs. 1, 2, and 3).

Oral and Subcutaneous Administration.—Thirteen patients received 1-hydrazinophthalazine by this route, but the results are clouded by the fact that 8 of these also received intravenous 1-hydrazinophthalazine. Only 5 patients received the drug purely by oral or subcutaneous administration.



COMPOSITE B. P. GRAPH OF RESPONSE TO INTRAVENOUS 1-HYDRAZINOPHTHALOZINE IN 29 PATIENTS

Fig. 1.

Dosage varied up to 160 mg. subcutaneously and up to 400 mg. orally per day. The results were inconclusive and varied. Two pre-eclamptic patients had a fairly good sustained hypotensive response. The blood pressure of the hypertensive patient with superimposed pre-eclampsia was held at 166/93 for 5 postpartum days on 400 mg. per day. After the fifth day the drug was discontinued and the blood pressure rose to an average of 188/112 and was at this level when the patient was discharged.

In general, it might be said that this form of therapy is not satisfactory at present due to the unpredictable response and the high percentage of failures when the dosage as outlined is used. Studies based on the employment of higher dosages are under way.

The one hypertensive pregnant patient listed as a failure was an extremely obese secundigravid white woman whose weight on admission was 286 pounds, blood pressure 170/100. Her response to subcutaneous and intravenous 1-hydrazinophthalazine was occasionally good, but in general

must be termed unsatisfactory. Dosage varied between 20 and 40 mg. subcutaneously every 4 to 6 hours and then 40 mg. intravenous doses every 6 hours, on one occasion she received 70 mg. of 1-hydrazinophthalazine over a 45 minute period. The diastolic pressure dropped below 90 with these dosages, but the systolic either responded little, not at all, or even rose 10 to 15 points. This patient obviously was resistant to the drug or its effects were not clinically apparent so far as blood pressure response was concerned. She did have the characteristic facial flush and tachycardia with bounding pulse, but the measurable indicator of response (blood pressure) did not decrease.

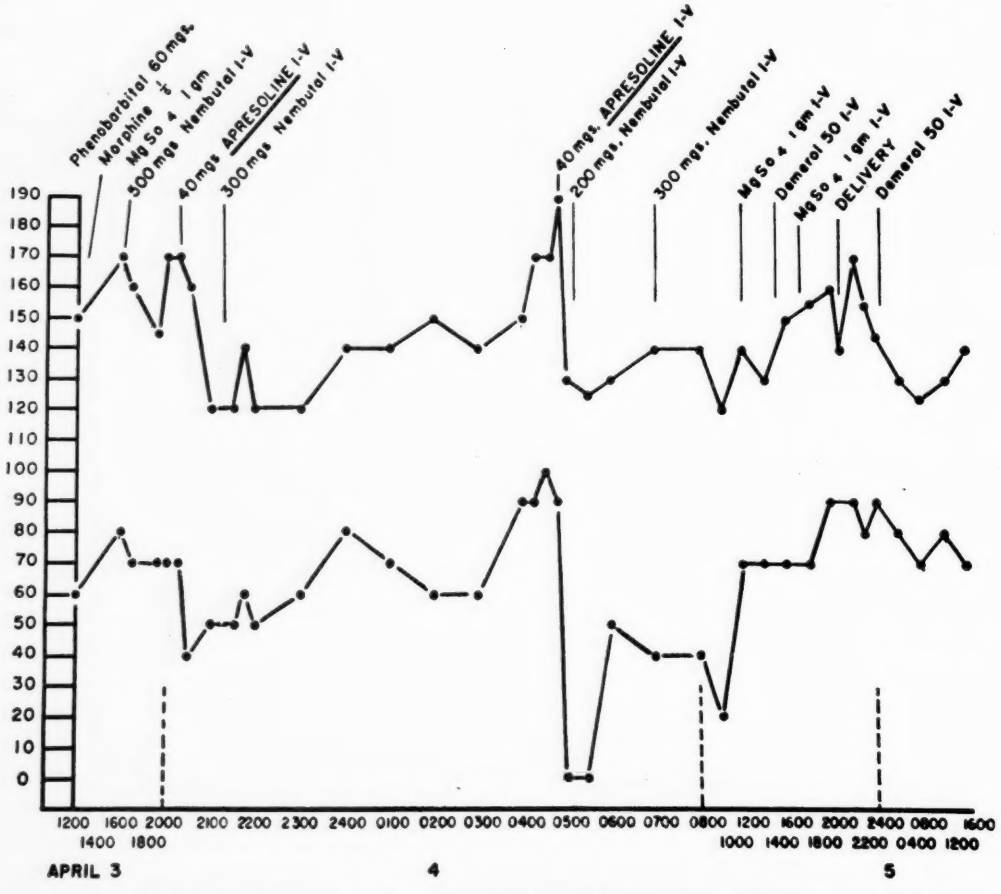
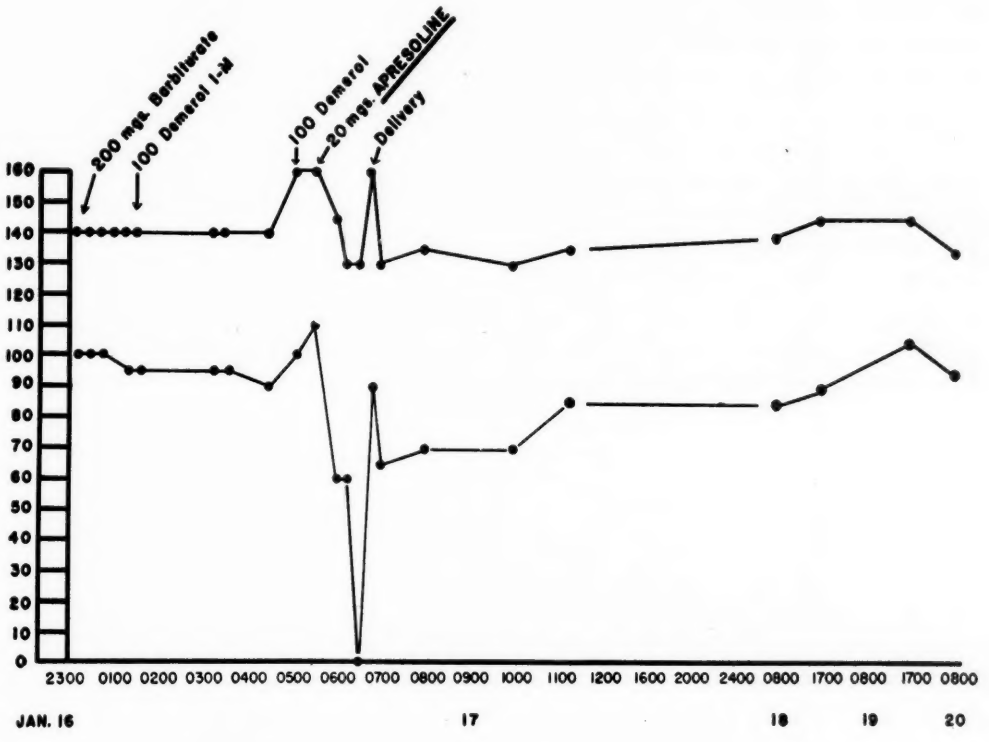


Fig. 2.

Other Effects.—Facial flush, tachycardia, and bounding pulse were evident in all patients who received the drug by the intravenous route. In fact we used these characteristic signs as an indicator of patient response to the drug. The onset of these occurred 5 to 15 minutes after the injection was begun and usually disappeared within 30 minutes to 2 hours.

A throbbing headache was occasionally evident, but in no patient did this necessitate the discontinuance of the drug. Yonkman and Freis[14] quote

Prandoni as stating that, "Such headaches could be corrected by extremely small doses of ergotamine tartrate (0.25 to 0.5 mg.)." They also quote Schroeder as stating, "Dramamine and other antihistaminic agents aborted and protected against this type of drug-induced headache." This has not always been found to be true. When Dramamine, Chlor Trimeton, or Pyribenzamine was used, no consistent effect on headaches was noted.[16]



HYPERTENSION IN LABOR
20 MG. I.V. HYDRAZINOPHTHALAZINE CASE 22

Fig. 3.

Comment

Until the etiological basis of the pregnancy toxemias is better established, it is obvious that therapy can be directed only toward symptomatic control of the disease. Use of an antihypertensive drug, such as 1-hydrazinophthalazine, only reduces the hypertension. But what is accomplished so far as the primary disease state is concerned is unknown. Previous studies showing that renal blood flow is increased make the clinical use of 1-hydrazinophthalazine more theoretically attractive than other drugs we have used. Further study concerning sodium excretion levels and the use of this drug is hopefully anticipated.

Although intake and output charts were carefully kept on all patients in this series, no diuresis of notable volume nor any overwhelming oliguric episode was recorded. Evaluation of these charts would be most difficult. Daily 24 hour albumin studies were performed. No effect could be demonstrated.

Eclampsia is notably absent in this series. There have been no cases at this institution since the initiation of this study. Whether the drug tends to inhibit its occurrence, or whether the drug will be effective in its treatment can hardly be commented upon at this time.

A reduction in the blood pressure should tend to prevent the mortality due to cerebral hemorrhage and edema coincident with toxemia and hypertension of pregnancy. Another major advantage in the use of such drugs as Apresoline or Veratrum is the lack of necessity for heavy sedation. These patients are thus more manageable and their infants less narcotized.

The blood pressure is reduced without a significant fall in cardiac output or pulse pressure. Even at maximum hypotensive levels, the pulse, though rapid, remained bounding and of good quality. There was no evidence of circulatory embarrassment. The fetal heart rate was unaffected. No other fetal effects were noted. No maternal analgesic or sedative effects were evidenced.

Summary

1. Results of clinical trial of 1-hydrazinophthalazine in 34 pregnant toxemic and hypertensive patients have been presented.

2. Vasodepressor response was achieved in all but one of the 29 patients who were given the drug intravenously.

3. Oral and subcutaneous administration did not result in uniform or satisfactory blood pressure response. This may have been related to dosage.

4. Theoretical basis for the advantages of this drug appears to be the increased renal blood flow with reduction in blood pressure and no decrease in cardiac output. No decrease in urinary output or increase in albuminuria was noted.

5. No claim concerning the reversal of the basic toxemic disease process is presented for this drug.

6. 1-hydrazinophthalazine is recommended for further trial in the control of the hypertensive aspects of pre-eclampsia and hypertension in the pregnant patient.

We wish to acknowledge the cooperation shown this department by Colonel T. W. Mattingly, Medical Corps, and Captain M. Moser, Medical Corps, of the Cardiovascular Section, in the use of this drug.

Apresoline (1-hydrazinophthalazine) for this work was contributed by Ciba Pharmaceutical Products, Inc.

References

1. Gross, F., Druey, J., and Meier, R.: Experientia **6**: 19, 1950.
2. Reubi, F. C.: Proc. Soc. Exper. Biol. & Med. **73**: 102, 1950.
3. Schmid, A., and Reubi, F. C.: Helvet. med. acta **17**: 543, 1950.
4. Reubi, F. C.: Helvet. med. acta **16**: 297, 1949.

5. Grimson, K. S., Chittum, J. R., and Metcalf, B. H.: Fed. Proc. **9**: 279, 1950.
6. Schroeder, H. A.: J. Clin. Invest. **30**: 672, 1951.
7. Schroeder, H. A.: Circulation **5**: 28, 1952.
8. Taylor, R. D., Page, I. H., and Corcoran, A. C.: Arch. Int. Med. **88**: 1, 1951.
9. Moyer, J. H., Handley, C. A., and Huggins, R. A.: J. Pharmacol. & Exper. Therap. **103**: 368, 1951.
10. Moser, M., Green, R., Orbison, J., and Mattingly, T. W.: The Use of Autonomic Blocking Agents in the Treatment of Essentital Hypertension, presented before Washington, D. C., Meetings of Am. Fed. for Clin. Research, November, 1952.
11. Hafkenschiel, J. H., Friedland, C. K., Yobaggy, J., and Jeffers, W. A.: Am. J. Med. **14**: 509, 1953.
12. Assali, N. S., and Suyemoto, R.: AM. J. OBST. & GYNEC. **64**: 1021, 1952.
13. Assali, N. S., Baird, W. W., Douglass, R. A., and Tioseco, E. L.: Am. J. Med. **14**: 491, 1953. (Abst.)
14. Yonkman, F. F., and Freis, E. D.: Angiology **3**: 36, 1952.
15. Assali, N. S., Oghenstein, S., and Suyemoto, R.: Hemodynamic Effects on 1-Hydrazinophthalazine (Apresoline) in Human Pregnancy. (To be published.)
16. Moser, M., and Mattingly, T. W.: Personal observations.

SEX PREDICTION THROUGH THE USE OF MATERNAL SALIVA

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IN 1951, Richardson[1] published a new biochemical test for pregnancy. Early results showed an accuracy approaching 100 per cent in known pregnancies. But the test was also positive in 50 per cent of the nonpregnant individuals. Further studies demonstrated the fact that two endocrine factors were the sources of the positive responses in the nonpregnant women. Richardson then developed an extractive method by which the interfering agents could be removed and was able to obtain approximately 100 per cent accuracy in both groups. The product of pregnancy which is identified by this is free estrone. Although present in nonpregnant women, its normal concentration is insufficient to give a positive reaction except in pregnancy, hydatidiform mole, and chorionepithelioma. The latter two, however, produce a positive reaction even in highly diluted urine.

Rapp and Richardson[2] investigated this test further and, in 1952, concluded that the reaction depends on the presence of free estrone in contrast to bound or modified estrone, or similar 17-ketosteroids. The free estrone level was found to increase markedly after conception so that positive reactions were obtained two weeks after fertilization and even before amenorrhea occurred.

In his original article, Richardson reported tests on such fluids as saliva, tears, and sweat, as well as blood and urine.

While the test on urine was positive in all women in the sixth or seventh month of pregnancy, it was negative in some of these when the saliva was tested. This lack of correlation was understandable after the birth of the child. It was found that in nearly every case where the saliva test proved positive, a male child was born and where negative, a female child was born.

The following table is reproduced from Richardson's report:

TABLE I. RELATION BETWEEN SEX OF CHILD AND REACTION OF THE MOTHER'S SALIVA TO THE RICHARDSON TEST

	POSITIVE	NEGATIVE
Males	218	3
Females	7	148

Richardson was unable to identify the substance responsible for the positive reaction, but believed that it was due to some androgenic substance. He felt that the maternal salivary glands could selectively transmit the androgenic type hormones while rejecting the estrogenic type.

Material

In attempting to confirm the work of Rapp and Richardson, we tested 200 patients at the prenatal clinic of the Harlem Hospital. The period of gestation of all patients tested was between 24 and 38 weeks and the heights of the fundi were between 24 and 36 cm. No patient who showed evidence of toxemia or infection was tested.

Technique

All tests were made in accordance with the technique described by Rapp and Richardson.[2]

All specimens of saliva were collected with the same precautions, i.e.:

1. No endocrine medication for 14 days before the test.
2. No medication whatsoever for 48 hours before the test.
3. The teeth were cleaned without a dentifrice and the mouth rinsed with clear water.
4. All patients reported to the hospital at 10:00 A.M. on the day of the test.
5. A ½ inch cube of paraffin was chewed for ten minutes and the saliva and paraffin discarded.
6. A second piece of paraffin was chewed again for ten minutes and about ½ ounce of saliva collected.
7. Nasal mucus and other abnormal mucus secretions were not collected.

Apparatus

The extraction apparatus* consisted of an outer standard screw cap test tube which was calibrated at the 2 c.c. and the 5 c.c. levels and an inner tube of slightly smaller diameter so that it could be inserted into the outer tube. The inner tube had a round hole safely above the 5 c.c. mark.

Reagents

Reagents used were prepared and standardized by the Chemistry Department of the Harlem Hospital and consisted of the following:

1. 0.5 Normal sodium hydroxide
2. Chloroform, U.S.P.
3. 0.5 Normal sulfuric acid
4. Saturated 2,4-dinitro-phenylhydrazine in 95 per cent ethanol.

Results

Of the 200 pregnant women whose saliva was tested, 109 males and 91 females were born. We had obtained positive reactions in 78 cases which should have resulted in male offspring. However, only 56 of these actually were males, while the remaining 22 were females. We had obtained negative reactions in 122 cases which should have resulted in females, whereas actually 69 females and 53 males were born.

This gave us an accuracy in predicting males of 73 per cent and in predicting females of 56 per cent. Our total number of errors was 75 cases or 32.5 per cent, giving us an average accuracy of 62.5 per cent.

*Purchased from the LaMotte Chemical Products Company.

Our findings are shown in Table II.

TABLE II. PREDICTED SEX IN RELATION TO ACTUAL SEX

RESULTS	NUMBER PREDICTED	ACTUAL SEX		ACCURACY OF PREDICTION	AVERAGE ACCURACY
		MALE	FEMALE		
Positive (predicted male)	78	56	22	73%	
Negative (predicted female)	122	53	69	56%	
Total	200	109	91		62.5%

Conclusions

1. The saliva of 200 women who were pregnant six to seven months was tested according to the technique of Rapp and Richardson.

2. The accuracy in predicting males was 73 per cent.

3. The accuracy in predicting females was 56 per cent.

4. The average accuracy was 62.5 per cent.

5. The accuracy of prediction so approximates mere chance that we do not feel that this test is of much value in its present state.

References

1. Richardson, Garwood C.: AM. J. OBST. & GYNEC. **61**: 1317, 1951.
2. Rapp, Gustav William, and Richardson, Garwood C.: Science **115**: 265, 1952.

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PENETRATING WOUNDS OF THE GRAVID UTERUS

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(From the Obstetrical Service of the Harlem Hospital)

IT IS not often that even a busy obstetrician is called upon to manage a penetrating wound of the gravid uterus. When the occasion does present itself, however, one must be prepared to act quickly and decisively in the best interest of at least two people. After assisting in the management of such a case and reviewing most of the recorded experiences of others, it appeared to us that a summary and analysis of these experiences might yield a modus operandi for the treatment of such accidents. Moreover, our case presented an apparent rupture of the fetal membranes, which subsequently healed; and the patient went on to term. This event is not infrequently imagined but is rarely proved.

Material

Twenty-three cases of penetrating wounds of the gravid uterus were taken from the world literature and summarized in Table I. To these is added our case, a detailed account of which follows. Two cases of perforation of the nongravid uterus, an even rarer accident, were not included in the summary but are a part of the discussion.

Case Report

W. M., a 20-year-old gravida iii, para ii, entered the hospital on May 12, 1952, approximately one hour after sustaining a knife stab wound of the abdomen. Her expected date of confinement was Sept. 29, 1952. The chief complaint upon admission was of generalized paroxysmal cramps "like labor pains."

Examination revealed that the patient was in no distress. Blood pressure, temperature, and pulse were normal. The hemoglobin was 75 per cent. The heart and lungs were normal.

Two centimeters above and just to the left of the umbilicus was a stab wound from which protruded a small piece of omentum. The abdomen was soft and only slightly tender. The fundus of the uterus extended 2 fingerbreadths above the umbilicus. There was no vaginal bleeding. A diagnosis of penetrating stab wound of the abdomen with probable injury of the gravid uterus was made, and surgical exploration advised.

Approximately 300 c.c. of blood was found in the peritoneal cavity. The uterus, estimated at 20 weeks' size, presented a 1.5 cm. laceration on the left anterior superior aspect. The wound was not bleeding actively, nor was there evidence of amniotic fluid about the wound. Moderate irritability of the uterus was noted. Finding no other visceral injury, the uterine wound was closed with two figure-of-eight sutures, and the abdomen was closed without drainage.

During the first twenty-four hours after surgery the uterine cramps increased, and a clear, watery fluid was seen escaping from the vagina. The suspicion of ruptured bag of waters was confirmed by the obstetrical consultant, and the patient was transferred to the maternity ward. There with antibiotics, sedation, and bed rest, the cramps subsided and the fluid drainage ceased by the third day. The remainder of the hospital course was uneventful. She was discharged on May 22, 1952.

After an entirely normal course in the prenatal clinic, the patient re-entered the hospital on Sept. 22, 1952, in active labor. Five and one-half hours after admission she spontaneously delivered a normal female child, weighing 6 pounds, 4 ounces. The membranes ruptured one hour before delivery, and the placenta separated easily after delivery. Following an afebrile postpartum course, the patient was discharged on Sept. 27, 1952. When seen in the postnatal clinic her condition was considered satisfactory.

Incidence

It is not possible to give the numerical incidence of penetrating wounds of the gravid uterus. This case is the only one in the records of the Harlem Hospital, despite the fact that we have a busy obstetrical service and a large part of the surgical material is caused by trauma. Thus, it seems safe to say that this accident is uncommon.

Etiology and Pathogenesis

Due to its enlargement and anterior position, the uterus may be easily damaged when the pregnant woman sustains a penetrating wound of the abdomen. The weapon used in the majority of the cases was a gun. Three cases, including ours, resulted from pointed weapons.

Even before the period of chemotherapy and antibiotics, infection was not a significant factor in the management of this type of injury. No cases of puerperal sepsis were reported. Storck,[19] who described an abdominal injury involving the nongravid uterus, attributes the lesser morbidity and mortality in the pregnant woman to the protection of the great vessels and small bowel offered by the enlarged uterus. This report supports his contention. Likewise, Bosts's[12] conclusion that the pregnant woman can withstand violent trauma and the gravid uterus itself is resistant to both trauma and infection seems as true today as it was years ago.

Pathology and Late Complications

In most instances the uterine wounds were localized and clean-cut. Three cases, however, those of Fudge,[2] Guadagnini,[9] and Zondek,[14] presented rather extensive destruction of the uterine wall. Zondek's case required wide débridement before adequate closure was effected. Nevertheless, all of the wounds were closed and the mothers recovered. Two cases required hysterectomy for the control of hemorrhage. In only 5 instances were the intestines perforated, and in only one of these was it necessary to resect the bowel.

The only maternal death that occurred in this series of 24 cases followed a perforation of the uterus without bowel injury. This death rate of 4.2 per cent compares favorably with the best results reported from World War II. Poer[20] gave a mortality of 17.7 per cent; while Sperling and co-workers[21] were able to salvage 86 per cent of their patients who had sustained perforating rifle- and pistol-shot wounds of the abdomen. The favorable influence of the gravid uterus is clearly seen.

The babies did not fare so well. Eleven survived the original accident and were delivered by cesarean section at the time of the operation or delivered spontaneously later. Hence, the fetal mortality is 54 per cent. Six of the 11 babies that survived presented injuries of various kinds.

Some of these patients were observed by their physicians over a period of years before the case was reported; therefore, the infrequency of late complications is significant. One patient underwent hysterectomy several months after the accident. The indication was intractable low abdominal pain. Endometriosis was not mentioned in any of the reports. Several patients went through subsequent pregnancies without difficulty. Zondek's[14] patient, despite extensive injury of the uterine wall, delivered spontaneously five years later and the placenta was not retained.

Alotin[22] described an accident involving a 19-year-old girl in Palestine. Shrapnel from an exploding bomb caused seven perforations of the small intestines, injury of the omentum, perforations of the uterus, rectum, and posterior vaginal wall. The left tube and ovary were completely destroyed. The damage was repaired, and eighteen months later the patient had a normal spontaneous delivery.

Diagnosis and Treatment

Usually, the diagnosis offers no great problem. In the patients reviewed the major vessels were not involved, and as the patients were rarely in deep shock, the history was readily obtainable. The position of the patient at the time of the accident may be important in the preoperative estimation of the structures damaged. In Belcher's[4] case the patient was shot while bending forward. The bullet entered the gluteal region and, apparently, perforated the uterus without damaging any other important structures.

Although 2 of these patients recovered without operative intervention, conservative surgery is the treatment of choice. In this series, 14 cesarean sections were performed with a total yield of only 7 live babies. The advisability of some of these sections is open to question.

In the 8 cases where the uterus was repaired without section, 4 went on to normal delivery and the babies survived. The intervals between injury and delivery varied from five days to four and one-half months. The remaining 6 cases, 4 nonsection and 2 nonoperative, were terminated by spontaneous abortion. Missed abortion, sepsis, abruptio placentae, and hemorrhage were never significant problems in the management of these cases.

There seems to be general agreement that the only absolute indication for cesarean hysterectomy is uncontrollable hemorrhage. This reason was given in the 2 cases above. Ligation of the uterine arteries should be attempted before hysterectomy is undertaken since it has been shown that hemorrhage can be controlled in this manner.

In 1941, Bost[12] indicated that section should be performed in these cases at almost any stage of pregnancy. There is little basis for such a stand today. During the first and second trimesters section per se is rarely indicated. The primary purpose of cesarean section, as in obstetrics generally, is to produce a live baby. When a section fails to accomplish this end the necessity for the operation requires justification. Of course, extenuating circumstances relative to the accident which threaten the life of the mother, as well as unrelated indications for cesarean section, may sometimes alter this position.

TABLE I. CASES OF PENETRATING WOUNDS OF THE GRAVID UTERUS REPORTED IN THE LITERATURE, 1910-1953

AUTHOR	WEAPON	GESTATION	TYPE OF INJURY	TREATMENT	RESULTS	
					MOTHER	BABY
Fowler[1] 1910	Gun	8 months	Perforation of uterus	Cesarean section and repair of uterus	Recovered	Survived, three fingers injured
Fudge[2] 1912	Gun	8-9 months	Portion of uterine wall shot away, fetus expelled into abdominal cavity	Uterine wall repaired	Recovered	Died, shot through pelvis and spine
Tucker[3] 1912	Gun	9 months	Perforation of uterus	Cesarean section and repair of uterus	Survived delivery, but died on postpartum da. 3	Sustained back injury, survived
Belcher[4] 1917	Gun	?	Perforation of uterus	Nonoperative	Recovered	Stillborn with bullet in head
Saint, Goehlinger, and Poire[5] 1920	Bursting shell	6 months	Perforation of uterus	Cesarean section and repair of uterus	Recovered	Back injury, neonatal death
Stiglbauer[6] 1924	Gun	?	Perforation of large and small bowels; bullet lodged in uterus	Cesarean hysterectomy, repair of intestines	Recovered	?
Placintianu and Turcanu[7] 1928	Gun	9 months	Bullet lodged in fundus of uterus	Bullet removed and uterus repaired	Recovered	Spontaneous delivery 17 days later with leg injury
Motta Maia and Vianna[8] 1929	Gun	Near term	Perforation of uterus, two perforations of ileum	Repair of bowel and uterus. Cesarean section	Recovered	Survived with injury of arm
Guadagnini[9] 1930	Dagger	8½ months	Laceration of anterior wall of uterus and herniation of placenta	Placenta restored and wall repaired	Recovered	Stillborn a few hours later, injury of right calf
Belknap[10] 1939	Gun	6 months	Perforation of uterus, hemorrhage	Hysterectomy	Recovered	Stillborn with bullet in chest
Badia and Charlton[11] 1940	Knife	7 months	Nonperforated wound of uterus	Repair of uterus	Recovered	Normal delivery at term
Bost[12] 1941	Gun	5 months	Two perforations of uterus, membranes intact, perforation of bowel	Cesarean section with repair of uterus and intestines	Recovered	Fetus uninjured, lived two hours

Camara and Casado[13] 1944	Gun	2 fingers above umbilicus	Perforation of uterus	Cesarean section with repair of uterus	Recovered	Died
	Gun	2 fingers above umbilicus	Perforation of uterus, 4 perforations of intestines	Cesarean section and repair of torn viscera	Recovered	Survived
Heinr	Gun	Near term	Perforation of anterior wall of uterus	Cesarean hysterectomy	Recovered	Survived
Morias	Gun	Early pregnancy	?	Nonoperative	Recovered	Abortion of traumatized fetus two months later
Ramirez	Gun	5 months	Perforation of uterus	Repair of uterus	Recovered	Fetus expelled 8 days later with compound fracture of left leg
Zondek[14] 1947	Bomb	Near term	Perforation of uterus with maceration of wound edges	Cesarean section and repair of uterus, wide débridement	Recovered	Asphyxia pallida, survived
Souter[15] 1947	Gun	7 plus months	Two perforations of uterus	Repair of uterus	Recovered	Normal delivery 5 days later, thigh wound
Holters and Daversa[16] 1948	Gun	8 months	Perforations of uterus and ileum	Cesarean section, repair of uterus and resection of 2 feet of bowel	Recovered	Stillborn, uninjured
Jacobus[17] 1952	Gun	4½ months	Perforations of uterus and ileum	Uterus and bowel repaired	Recovered	Aborted 8 days later
Popadopoulas[18] 1953	Gun	8 months	Perforation of uterus	Cesarean section and repair	Recovered	Stillborn
	Gun	8½ months	Perforation of uterus	Cesarean section and repair	Recovered	Survived
Wright, Posner, and Gilchrist this report 1953	Knife	4½ months	Perforation of uterus	Repair of uterine wall	Recovered	Normal delivery at term

Summary

Twenty-three cases of penetrating wounds of the gravid uterus have been summarized and analyzed. An additional case from our records has been described. The evidence gained from these cases favors conservative surgery as the treatment of choice. In addition, our case offers strong evidence that the fetal membranes are sometimes capable of resealing themselves if they are ruptured prematurely.

Addendum.—Since this paper was prepared, four cases of shrapnel wounds of the gravid uterus have appeared in a foreign journal,[23] incident to World War II. The first three patients were sectioned and two babies died. The fourth was not operated upon and the baby survived with permanent injury of one hand. All the mothers survived without sequelae.

References

1. Fowler, R. S.: New York State J. Med. **11**: 525, 1911.
2. Fudge, H. W.: J. A. M. A. **58**: 779, 1912.
3. Tucker, A. W.: J. A. M. A. **58**: 1685, 1912.
4. Belcher, Clement: Brit. M. J. **1**: 896, 1917.
5. Saint, Goehlinger, and Poire: Progrés méd. Paris **31**: 196, 1920.
6. Stiglbauer, R.: Wien. klin. Wchnschr. **37**: 69, 1924.
7. Placintianu, G., and Turcanu, G.: Spitalul **48**: 224, 1928.
8. Motta Maia and Vianna, G.: Rev. de gynec. e d'obst. **23**: 319, 1929.
9. Guadagnini, A.: Rev. méd. latino-am. **15**: 1029, 1930.
10. Belknap, R. W.: J. Maine M. A. **30**: 13, 1939.
11. Badia, P. D., and Charlton, A.: New York State J. Med. **40**: 1797, 1940.
12. Bost, T. C.: South. M. J. **34**: 1040, 1941.
13. Camara, A., and Casado, L.: Rev. méd. panam. **1**: 203, 1944.
14. Zondek, B.: Lancet **1**: 674, 1947.
15. Souter, R. J. deN.: M. J. Australia **34**: 111, 1947.
16. Holters, O. R., and Daversa, B.: Am. J. Obst. & Gynec. **56**: 985, 1948.
17. Jacobus, W. N.: Am. J. Obst. & Gynec. **63**: 687, 1952.
18. Popadopoulas, J.: Mém. Acad. chir. Paris **78**: 10-11, 1953.
19. Storck, A. H.: Ann. Surg. **111**: 775, 1940.
20. Poer, David H.: Ann. Surg. **127**: 1092, 1948.
21. Sperling, L., Basher, L. H., and Zimmerman, H.: Surgery **21**: 258, 1947.
22. Alotin, A.: Harefuah **28**: 195, 1950.
23. Rautureau, M., and Ducourneau, E.: Bull. Fed. soc. de gynéc. et obst. **5**: 26, 1953.

ABNORMAL VAGINAL BLEEDING. I.

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(From the Group Health Association)

THE diagnosis of functional uterine bleeding as it is generally used gives the impression that it is a specific condition for which there is a specific treatment. This is not so. In summarizing the management of 490 women with sufficiently abnormal bleeding, not associated with pregnancy, to warrant at least one diagnostic curettage, I find that I have abandoned the word "functional." Although the initial vaginal examination of each of these individuals revealed no gross lesions, subsequent observation for two to seven years has resulted in a definite diagnosis pertinent to the problem in 166 women as shown in Table I.

TABLE I

Malignant neoplasm	19
Nonmalignant neoplasm	41
Senile vaginitis	49
Emotional disturbance	34
Thyroid disorder	14
Purpura	6
Hypertension	3

To class these 166 individuals as having "functional" cases of bleeding would be obviously incorrect, especially if such a diagnosis led to intensive hormone treatment. In some of the instances of malignancy the diagnosis might be delayed by such a program. The nature of the 59 neoplastic conditions is shown in Table II.

TABLE II

Adenocarcinoma of corpus	10
Carcinoma of ovary	3
Squamous carcinoma of cervix	3
Carcinoma of breast	3
Submucous myoma	8
Interstitial myoma	25
Adenomyosis	3
Endometriosis	3
Serous cystoma of ovary	1

Women with abnormal bleeding are divided into three groups to decide when diagnostic curettage is necessary. The first is postmenopausal. Any degree of bleeding in this group is considered sufficient indication. The second includes women past 35 with pronounced increase in menstrual flow or intermenstrual bleeding, or both, persisting beyond two or three successive cycles. It is of interest to note that each neoplasm reported in Table II

occurred within these two groups. In not one instance in the third group, made up of 18 individuals under the age of 35, was a serious condition found. In this younger group, when a menstrual irregularity occurs, I am more concerned about the woman's general health than about the likelihood of a gynecologic condition. After thyroid disorder, tuberculosis, and blood dyscrasia have been ruled out, it is my customary policy to reassure the individual that I am certain it cannot be anything serious. I perform curettage more for the reassurance value of a negative tissue test than for any other reason. In 17 of these younger women emotional stress factors may have been the aggravating influence. Only one was in the adolescent age, a child of 10, with what appears to be a moderately precocious puberty.

When abnormal bleeding appears in a woman taking estrogenic hormones it is usually the estrogen that is responsible and when this is discontinued the bleeding will usually subside in two or three weeks. If it persists for a longer period of time it is best to perform a curettage.

Diagnoses, other than neoplasm, may not be readily apparent unless one makes it a habit to search for them. Senile vaginitis is commonly overlooked.[1] I have seen women who were subjected to unnecessary surgery and irradiation because of a bloody postmenopausal vaginal discharge from undiagnosed senile vaginitis.

Emotional disturbances associated with abnormal menstrual bleeding were found in 9 per cent of the women in this report. Some physicians may consider this too high, others too low, depending upon their background in psychiatric experience. The physician who is interested enough to seek will find them. It does not require psychoanalytic technique to uncover an alcoholic husband, a pressing domestic situation, or a lover who has deserted. I know one woman who bled to a hematocrit of 22 when thwarted in her career, and another who did likewise when she discovered that her fiancé had married someone else.

Three of the 14 women listed under thyroid disorder have definite myxedema. The others have normal metabolism and no symptoms except that on a small daily dose of thyroid their menses are regular, without it they are excessive and prolonged.

The 6 women with purpura and 3 with hypertension have no other abnormalities. The excess bleeding coincides with flare-up in the medical condition and it is assumed there is a connection.

The real problem is what to do with the woman who continues to bleed abnormally. We cannot find a neoplasm or any other condition that may be aggravating her condition. Month after month she continues to bleed without relief. My customary procedure is to advise the woman, after the curettage has been performed, that there is nothing we need be concerned about except the degree of inconvenience the bleeding causes. When really excessive menstrual bleeding continues for longer than four to six months I advise an elective hysterectomy be performed to check it. Some women will put up with the bleeding to save the uterus even to the point where an

occasional blood transfusion has to be given to keep the count near normal. If the woman desires more children the best thing to do is become pregnant.

I do not employ hormones to treat abnormal bleeding except when it is due to senile vaginitis. I have used estrogens and other sex steroid hormones for a variety of female disorders since I originally became interested in stilbestrol at a time when it could be obtained only for investigative purposes.[2] I have yet to discover a method of administration of hormones that will control abnormal menstrual bleeding. In some instances estrogen appears to increase the bleeding. For the past three years my procedure has been curettage followed by observation. If anemia is present, naturally it needs attention. Dr. Emil Novak[3] calls this attitude nihilistic. Perhaps it is, but in seven years I have had to employ radical measures in 33 of the 324 individuals so managed. This is 10 per cent. Every one of these women is over 35 years old. The remaining 90 per cent have had sufficient spontaneous remission to allow them to carry on their normal activities.

I consider elective hysterectomy the procedure of choice today to stop excessive bleeding, chiefly because the ovaries can be spared. I have several women patients with unusually severe menopausal symptoms plus dyspareunia from constrictive senile vaginitis as a consequence of irradiation.[1, 4] In a poor surgical risk irradiation may be used, but with sufficient blood for transfusion and modern anesthetic technique the number of poor-risk patients appears to be at a vanishing point. About the only thing I can say in favor of irradiation is that for a busy working woman with little time to spare it is convenient. This represents a tremendous change in attitude on my part as I formerly considered intracavitary radium the treatment of choice.[5]

To summarize, in a group of 490 women who manifested abnormal vaginal bleeding, a definite diagnosis has been made by diagnostic curettage and observation in 166. Ten per cent of the remaining 324 individuals have continued to bleed in sufficient degree that it was necessary to terminate their menstrual function by surgery, irradiation, or both. The other 90 per cent have had sufficient spontaneous remission to carry on without any other treatment than iron and vitamins for secondary anemia when present. Hysterectomy appears preferable to irradiation when termination is necessary.

References

1. Bieren, R.: M. Ann. District of Columbia **19**: 608, 1950.
2. Compton, B. C., and Bieren, R. E.: Bull. School Med. Univ. Maryland **26**: 130, 1941
3. Novak, Emil: Obst. & Gynec. Surv. **7**: 536, 1952.
4. Bieren, R.: M. Ann. District of Columbia **20**: 478, 1951.
5. Bieren, R. E., and Hundley, J. M., Jr.: Am. J. Obst. & Gynec. **54**: 321, 1947.

CLINICAL STUDIES CONCERNING THE RELATIONSHIP OF ESTROGENS TO THE DEVELOPMENT OF CANCER OF THE CORPUS UTERI

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IN MORE recent years several publications have dealt with the problem of the possible connection between estrogens and cancer of the corpus uteri. The assumption of such an interaction between estrogens and endometrial cancer has found support partly in experimental observations,[5, 11] and more particularly in clinical experiences.[1, 2, 4, 6, 7, 8, 9, 12, 13, 15, 17, 18, 19]

For a number of years we have taken great interest in this question. So, in order to gather additional information through clinical studies, our patients admitted with endometrial cancer have been thoroughly examined with regard to the following features:

1. The time of the onset of the menopause.
2. Possible previous menstrual disturbances.
3. Presence of climacteric symptoms of ovarian deficiency.
4. Marital status and fertility.
5. Histological picture of the possibly noninvaded part of the endometrium.

Finally, as the most important question in this investigation:

6. Intensity and duration of any estrogen therapy given.

Material

The present study includes all the patients who were admitted from 1939 to 1952 to the Gynecological Department of the Frederiksberg Hospital, and in whom the diagnosis of cancer of the corpus uteri was established—a total of 82—together with the patients who, in the period between 1943 and 1950, were under treatment for this lesion in the Surgical Department of the Aalborg Kommune Hospital, altogether 23 patients. This makes a total of 105, representing practically all the patients who entered the two hospitals with cancer of the corpus uteri within the periods mentioned.

For the sake of comparison a control series was studied consisting of 52 patients admitted to other departments of the hospitals for diseases which could not conceivably have had an influence upon the outcome of the questions here examined. All these control patients had passed the menopause, on an average of 11.5 years before, and none of them had previously had any abdominal lesion.

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Results

Age Distribution.—From Table I the age distribution of the patients studied is evident. It will be noticed that the majority of the patients were found in the age group of 51 to 60 years. Altogether 64 patients (61 per cent) were between 46 and 60 years of age. The average age of the patients at the time of first admission was 55.8 years.

TABLE I. AGE DISTRIBUTION OF THE PATIENTS

AGE (YEARS)	31-40	41-50	51-60	61-70	71-80	Total
No. of patients	5	27	45	16	12	105

Onset of Menopause.—Seventy-two patients had passed the menopause, that is, 68.6 per cent. The average age at the onset of the menopause for these 72 patients was 49.6 years. Only patients with a history of cessation of periods for at least one year were included in this calculation. In the control material the menopause occurred at an average age of 47.9 years, i.e., about 1.7 years earlier than in the patients with cancer of the corpus.

Preceding Abnormalities of Uterine Bleeding.—Among the 72 postmenopausal patients with cancer of the corpus uteri, information was obtained in 64 cases about menopausal bleeding. Of these patients, 20 (31.3 per cent) gave a history of abnormal bleeding, principally in the form of metrorrhagia. Only 9 of the 52 controls (17.3 per cent) had had disturbances of bleeding during the menopause, generally in a considerably milder form. A feature illustrating the difference in the bleeding intensity in the two groups of patients is found, among other things, in the fact that 20 of the cancer patients with abnormal bleeding in or about the menopause had been submitted to curettage for the condition, 7 of them on two occasions. Only 3 out of the 9 controls with metrorrhagia during the menopause had been curretted and none more than once.

Symptoms of Ovarian Deficiency.—In 79 of the patients with a diagnosis of cancer, 31 (39.2 per cent) claimed not to have had any complaints whatever, whereas only 10 (19.2 per cent) of the controls were able to give such a history.

Marital Status and Fertility.—Of the total cancer patients, 28 (28 per cent) of the 100 whose marital status is known had never been married. Data on the number of births were obtainable in the cases of 69 of the 72 married patients. Of this number, 14 (19.4 per cent) had never had any children while the remaining 55 together had given birth to 125 children, an average of 2.3 children per married patient.

Histological Picture of the Apparently Normal Part of the Endometrium.—It has been emphasized previously (Novak and Yui[15]) that the appearance of cystic glandular hyperplasia in the presence of cancer of the corpus uteri is a frequent observation. In the present material, the microscopic sections from 25 of the patients were examined in regard to the contemporary occurrence of these two pathological conditions. These 25 specimens were the only ones accessible, and all originated from patients who had never received estrogens.

In the specimens of 12 of these patients, most of whom were treated surgically, the examination revealed the presence of noninvaded endometrium.

In 2 of these cases the specimen showed quite small and scattered glandular lumina lined with inactive epithelium, located in stroma comprised of small cells corresponding to that of a senile mucous membrane.

In 3 cases the specimens showed areas of tissue that had been designated as polyps or parts of polyps, roundish areas of tissue with larger or smaller irregular glandular lumina lined with a lower inactive epithelium and located in a fibrous stroma with coarse vessels.

In 5 cases the sections presented areas with inactive stroma and larger cystically dilated glandular tubes lined with inactive epithelium—often adjacent to other areas presenting features of tumor tissue. Fig. 1 shows a picture typical of the findings in these 5 cases.

This picture can hardly be said to represent the presence of cystic glandular hyperplasia, as no doubt the changes demonstrated are to be interpreted as senile ones.

Finally, in 2 cases sections have shown the presence of true cystic glandular hyperplasia, the prerequisites of this diagnosis being a tissue rich in cells, active stroma, and highly active glandular epithelium made up of cells of the proliferating type with mitoses.

Exogenous Estrogenic Effect.—Among the patients from whom such information was available, 33.2 per cent had received estrogens in varying amounts. Among the patients of the control material, only 21.1 per cent had ever received any kind of hormonal treatment.

TABLE II. INCIDENCE OF THE FEATURES EXAMINED IN CANCER PATIENTS AND IN THE CONTROLS

	AVERAGE AGE AT ONSET OF MENOPAUSE (YEARS)	METRORRHAGIA PRIOR TO THE MENOPAUSE	NO CLIMACTERIC COMPLAINTS	STERILITY	PATIENTS TREATED WITH ESTRIN
Cancer patients	49.6	31.3%	39.2%	19.4%	33.2%
Controls	47.9	17.3%	19.2%	Approx. 10%	21.1%

Estrogen-treated Patients With Cancer of the Corpus Uteri.—In Table III a schematic survey is given of 16 patients suffering from cancer of the corpus uteri who, prior to the diagnosis, had been treated with large doses of estrogenic hormone. In the majority of these cases the hormonal treatment had been protracted and continuous. As a rule the daily dose was fairly moderate, but there can be no doubt that it was sufficient in the course of time to cause a not inconsiderable stimulation of growth of the uterine mucosa. In this connection it may be mentioned that, in a case reported by Clemmesen,[1] in which stilbestrol therapy had brought about such vigorous hyperactivity and cellular polymorphism that the endometrial hyperplasia resembled adenocarcinoma, the stilbestrol dosage had been 0.3 mg. daily. Such a dosage, presumably, had been exceeded in all the cases presented here.

The average age of the 16 patients entered in Table III was 55.1 years.

The diagnosis, often difficult in estrogen-treated cases, was made by Dr. L. Heerup, Chief Pathologist, Frederiksberg Hospital. In 12 of the 16 cases the histological picture of the specimen was unquestionably malignant, with invasive growth. In the remaining 4 cases (Nos. 2, 10, 13, and 15) there was some doubt as to whether we were dealing with an instance of hyperproliferation with nuclear atypia produced by the estrogen therapy or a case of early adenocarcinoma; the final diagnosis was made only after a repeated diagnostic curettage, 3 to 6 weeks after the cessation of estrogen therapy.

Fig. 1.—Uterine biopsy from the corpus uteri. Above, to the right, indisputable tumor tissue; below, transition to a large area showing cystically enlarged, inactive glands. (×90; reduced ⅙.)

In order to find out whether the hormonal therapy during the menopausal may have promoted the development of cancer of the corpus uteri, we obtained a patient group comparable with the hormone-treated group by excluding the following patients:

A. Patients whose tumor was diagnosed prior to the menopause.

B. Some patients who had received hormones but who were not included in the group surveyed in Table III.

C. Those in whom the menopause dated further back than the earliest menopause recorded in the hormone-treated patients (Table III, 1932). Exclusion of these patients left altogether 20 patients who had not received hormonal treatment and in whom the presence of the tumor was diagnosed within the same period as in the estrogen-treated patients. The average age of these 20 patients was 57.4 years, or 2.3 years more than the average age of the 16 estrogen-treated patients. On the other hand, the period from the first onset of the menopause to the time of the diagnosis of the tumor showed no difference, as it was 6.9 years for the non-hormone-treated patients and 7.4 years for the hormone-treated.

TABLE III. SURVEY OF 16 ESTROGEN-TREATED PATIENTS WITH CANCER OF THE CORPUS UTERI

CASE NO.	AGE AT TIME OF DIAGNOSIS	AGE AT MENOPAUSE	BLEEDING ABNORMALITIES BEFORE MENOPAUSE	ESTROGEN THERAPY	
				DURATION IN YEARS	DAILY DOSE IN MG.
1	65	49	-	6	Stilbestrol 0.4
2	50	47	-	2.5	Stilbestrol 0.5
3	52	46	7 months. Curettage, x-rays	5	Stilbestrol 0.3
4	52	46	-	4	3 estrin tablets
5	55	47	-	6	Stilbestrol 1.0
6	54	52	8 months. Curettage, x-rays twice	2	Stilbestrol 0.3
7	53	-	3 years (metrorrhagia)	2	Stilbestrol, etc.
8	54	50	3 months. Curettage, x-rays	1.5	Ovex injections
9	57	50	-	6	Stilbestrol 0.5-1.0
10	55	52	6 years. Curettage, x-rays twice	3	Stilbestrol } 0.5-1.0 Hexestrol }
11	51	49	-	3	3 estrin tablets
12	50	48	-	9	Stilbestrol, Hexestrol, Ovex injections
13	57	49	-	8	Dienestrol 1.5
14	57	40	-	15	Stilbestrol 1.0
15	54	42	-	15	Stilbestrol, Dienestrol 1.0-1.5
16	66	51	Curettage and x-rays at age of 51	15	Stilbestrol 0.5

Comment

Our studies have shown that the menopause appears late in the patients with cancer of the corpus uteri, and also that pathological bleeding frequently occurs in connection with the climacteric. This is taken to signify that many of these patients have been liable to a more vigorous and more protracted endogenous estrogenic activity than is the average for women in this age group. In keeping with this, Corscaden and Gusberg[2] found the menopause to be late in patients with cancer of the corpus uteri and, as in our material, menopausal bleeding occurred about three times as often among these patients as in the control material.

The menopausal symptoms are generally considered to result primarily from the altered hormonal balance in the individual. It is a general experience that these complaints subside to a great extent after treatment with estrogens, and it seems obvious to assume that patients with cancer of the corpus uteri generally have a higher estrogen level when they have been free from this kind of complaint twice as often as have the patients in the control material.

The phenomenon that appears to be rather constant in patients with cancer of the corpus uteri is the relatively frequent state of sterility. Among other authors, Corscaden and Gusberg observed this feature in their material, and it is found in the present study also. The cause of this has been thought to be the occurrence of a great number of anovulatory cycles in these patients, which again would give rise to longer periods of constant estrogen stimulation and in this way, perhaps, promote the development of endometrial carcinoma.

Generally the histological picture of the endometrium indicates the hormonal balance of the organism, and it might appear rational, as done by Novak and Yui,[15] to examine nonmalignantly transformed endometrium from

patients with cancer of the corpus uteri. Among 104 cases these authors found in 64 patients noninvaded parts of endometrium and in 25 of the latter they found a simultaneous state of cystic glandular hyperplasia. Novak and Yui think that the cystic glandular hyperplasia appearing during the menopause predisposes toward cancer of the corpus uteri. Payne[16] has been unable to confirm the findings reported by Novak and Yui; and Fahlund and Broders[3] found atrophic endometrium twice as frequently in patients with endometrial carcinoma as in a control series. Kottmeier[10] found that polyps in the uterine cavity and adenocarcinoma often occur together, whereas a uterine mucosa with distinct evidence of estrogenic activity is seen but seldom. The views of the pathologists differ as to where the border line is to be drawn between senile endometrium with dilated glands and cystic glandular hyperplasia, and for that reason investigators fail to reach agreement. The difficulty in distinguishing between polyps in the corpus uteri and cystic glandular hyperplasia is even greater.

In this connection it is to be mentioned that several investigators (e.g., Meyer,[12] Taylor,[17] Novak and Yui,[15] Gusberg[6]) have described gradual transitions from typical cystic glandular hyperplasia to typical adenocarcinoma. No such transition has been encountered in our series, a fact which naturally may be due to the small size of the group, but also to the fact that the criteria adopted in our studies for the designation of cystic glandular hyperplasia differ from those employed by other authors. Fig. 1 shows a case in which endometrium with normal but inactive glands is seen to present a definite transition to a malignant tumor. This picture appears to correspond to the one designated by Novak[14] as a transition from cystic glandular hyperplasia to tumor, but this view does not seem justifiable if we wish to maintain that the mucous membrane must present an active stroma and epithelium in such cases.

The outcome of the endometrial examinations in our series appears to be in keeping with Kottmeier's[10] statements. The fact that cystic glandular hyperplasia and endometrial cancer are not particularly concurrent cannot be claimed decisively to discredit the theory about an etiological connection between estrogens and cancer of the corpus uteri, inasmuch as usually a certain length of time elapses between the commencement of the tumor and the time of its diagnosis. During this period the hormonal balance may have altered decisively which in turn will be reflected in the functional condition of the endometrium.

Various authors (e.g., Hodgson, Dockerty, and Mussey[8] and Mussey, Dockerty, and Masson[13]) call attention to the fact that patients with theca- and granulosa-cell tumors, which are hormone producers, develop cancer of the corpus uteri about 100 times more often than would be expected, and that this tumor growth often is accompanied by a state of cystic glandular hyperplasia. This observation, in view of the fact that, as far as is known, no instance of cancer of the corpus uteri has ever been reported in patients who had had an oophorectomy prior to the menopause, lends considerable support to the theory that estrogenic substances influence the development of endometrial cancer.

The preceding discussion has been chiefly concerned with the evidence afforded by clinical observations as to the significance of endogenous estrogen production in the development of cancer of the corpus uteri. What follows is the consideration of the role played by the exogenous administration of estrogens.

In spite of the relatively infrequent occurrence of menopausal symptoms in cancer patients which, as already mentioned, is suggestive of a higher estrogen level in such patients than in the controls, it still remains an outstanding fact that they had been given estrogen therapy more often than had the controls. Furthermore, in the cancer patients so treated the estrogen therapy in general has been more energetic, protracted, and continuous than in the control patients. Thus, the patients entered in Table III were given continuous estrogen therapy through 1.5 to 15 years (average 6.5 years) which, without further documentation, may safely be said to exceed considerably the average amount of estrogen given therapeutically to menopausal women.

Case reports have been published[4, 6, 7, 18, 19] in which endometrial carcinoma developed subsequent to, or during treatment with, estrogenic substances in the menopause; the respective authors thought there existed some connection between the estrogen therapy and the development of the adenocarcinoma in the uterus. The rather scanty number of case reports of this kind published up to now suggests that such an interaction has not often been taken into consideration. However, among our 105 cases, as is evident from Table III, no less than 16 appear to furnish evidence that the administration of hormones played some role in the development of the tumor. At any rate, in these patients the tumor developed in direct relation to the hormonal treatment.

Patients Nos. 5, 11, 12, 14, 15, and 16 in Table III had been troubled with vaginal bleeding for several years with intervals of a few months. It is not very likely that an endometrial cancer was present through these long periods. In view of the intensity of the hormonal dosage and the character of the bleeding, it seems far more probable that the cancer had developed in a continuously active and proliferating mucous membrane. In Case 5 this view was established almost with certainty, as a previous curettage, performed a couple of years prior to the diagnosis of the cancer, had shown cystic glandular hyperplasia. Novak and Ingram[9] found a similar clinical picture presented by 70 per cent of their patients with estrogen-producing ovarian tumors and cancer of the corpus uteri.

It is to be emphasized that in 4 patients (Cases 2, 10, 13, and 15) the differential diagnosis between hyperproliferation due to the estrogen therapy and the early stage of carcinoma was rather difficult. Not until the administration of estrogen had been discontinued and histological examination had been repeated, after an observation of 5 to 6 weeks, could the diagnosis be made. We have observed several such cases in which a cancerlike hyperproliferation after estrogen therapy subsided on cessation of this treatment. Of course, such cases have not been included in the present material. In Case 14

(Table III), after treatment with estrogen through 15 years, curettage was performed two years prior to the present admission on account of metrorrhagia. Histological examination showed an endometrium with hyperactivity and hyperproliferation and moderate nuclear atypia (changes possibly due to estrogen therapy?). There was no definite sign of malignancy. During the following observation, in spite of the cessation of the estrogen therapy, the patient continued to have vaginal bleeding for a few days every few months. Then she failed to return for further examination. On her present admission, examination showed a large adenocarcinoma with invasive growth. It is probable that the histological picture which two years before was taken to present an estrogen-overstimulated mucosa actually was an early carcinoma. These cases, and in particular Case 14, illustrate how poorly defined and blurred the borders may be between the histological picture of the estrogen-overstimulated mucosa and uterine adenocarcinoma.

Even though in the present study the tumor made its appearance on an average 2.3 years earlier in the hormone-treated patients, there is hardly sufficient evidence in this material for the assumption that the estrogens have exerted an accelerating effect upon the development of the tumor.

Clinical observations of endometrial carcinoma developing in a strikingly large number of cases after protracted endogenous or exogenous estrogenic stimulation find additional support in some experimental results which lend support to the theory of the influence of estrogens upon the development of tumors in certain organs: Lacassagne[11] has demonstrated the significance of estrogens to the development of cancer of the breast in mice; and by the administration of estradiol benzoate Gardner[5] has been able to produce cancer of the uterine cervix in mice.

In the material here studied the clinical observations appear to show that the endogenous estrogen production as well as exogenous estrogen supply in the menopausal patient play a role in the development of endometrial carcinoma. No findings were noted to contradict this view.

The logical conclusion of this must be that a certain degree of caution has to be exercised in the employment of estrogens during and, in particular, after the menopause. A protracted and continuous dosage should be avoided. The milder sedatives are often sufficient for the treatment of menopausal deficiency complaints. If estrogenic treatment is considered essential, however, these substances should be given periodically, with intervals sufficiently long for the endometrium to arrive at the resting stage. If under such a regimen hemorrhagic disturbances appear, the treatment can with advantage be combined with androgens or sometimes the latter can be employed alone.[20] This management of such cases does away with the continuous growth-stimulating effect upon the endometrium, which presumably constitutes the fertile soil in which certain cases of endometrial cancer develop.

Summary

A total of 105 cases of endometrial carcinoma are studied with regard to (1) age at the onset of the menopause; (2) preceding periods of metrorrhagia;

(3) presence or absence of menopausal complaints; (4) marital status and fertility; (5) histological picture of the possibly apparently normal part of the endometrium; (6) intensity and duration of estrogen therapy possibly given.

The present studies show that in these cancer patients the menopause commences later and is more often preceded by periodic metrorrhagia, and less frequently accompanied by hot flushes, indicating that these patients have often been under the influence of endogenous estrogens through longer periods than the average woman. The women in this series suffering from cancer of the corpus uteri have often given a history of treatment with estrogens in a larger amount and for a longer duration than was recorded for the controls. Thus 16 of the cancer patients had had continuous treatment with estrogens for from 2 to 15 years (average 6.5 years, Table III).

The difficulty in making the histological diagnosis in such cases is pointed out; and it is emphasized that in dubious cases it is essential to keep the patient under observation for a few months without administration of any estrogen before a conclusive biopsy can be performed. During this interval, in some instances a cancerlike hyperplasia of the endometrium will disappear.

The conclusion is drawn that a continuous estrogenic stimulation (endogenous or exogenous) constitutes an important factor in the etiology of endometrial cancer.

Precautions concerning estrogen therapy in the menopause are emphasized.

References

1. Clemmesen, J.: Acta obst. et gynec. Scandinav. **27**: 384, 1948.
2. Corscaden, J. A., and Gusberg, S. B.: Am. J. Obst. & Gynec. **53**: 419, 1947.
3. Fahlund, G. T. R., and Broders, A. C.: Am. J. Obst. & Gynec. **51**: 22, 1946.
4. Fremont-Smith, M., Meigs, J. V., Graham, R. M., and Gilbert, H. H.: J. A. M. A. **131**: 805, 1946.
5 Gardner, W. U., Allen, E., Smith, G. M., and Strang, L. C.: J. A. M. A. **110**: 1182, 1938.
6. Gusberg, S. B.: Am. J. Obst. & Gynec. **54**: 905, 1947.
7. Henry, J. S.: Canad. M. A. J. **53**: 31, 1945.
8. Hodgson, J. E., Dockerty, M. B., and Mussey, R. D.: Surg., Gynec. & Obst. **81**: 631, 1945.
9. Ingram, J. M., and Novak, E.: Am. J. Obst. & Gynec. **61**: 774, 1951.
10. Kottmeier, H. L.: Acta obst. et gynec. Scandinav. (supp. 6). **27**: 1, 1947.
11. Lacassagne, A.: Compt. rend. Acad. d. Sc. **195**: 630, 1932.
12. Meyer, R.: Ztschr. f. Geburtsh. u. Gynäk. **88**: 441, 1923.
13. Mussey, E., Dockerty, M. B., and Masson, J. C.: Proc. Staff. Meet., Mayo Clin. **23**: 63, 1947.
14. Novak, E.: Gynecological and Obstetrical Pathology, Philadelphia, 1941, W. B. Saunders Company, pp. 207-209.
15. Novak, E., and Yui, E.: Am. J. Obst. & Gynec. **32**: 674, 1936.
16. Payne, F. L.: Am. J. Obst. & Gynec. **34**: 762, 1937.
17. Taylor, H. C.: Am. J. Obst. & Gynec. **23**: 309, 1932.
18. Terp, A.: Ugeskr. f. læger. **112**: 1289, 1950.
19. Vass, A.: Am. J. Obst. & Gynec. **58**: 625, 1949.
20. Østergaard, E.: Acta obst. et gynec. Scandinav. **30**: 106, 1950.

CARCINOMA OF THE FALLOPIAN TUBE DETECTED BY CERVICAL SMEAR

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CARCINOMA of the Fallopian tube is one of the rarest neoplasms of the female genital tract. Up to 1952 the total number of cases reported was 503.[1] In the surgical pathology material at the Vancouver General Hospital during the five-year period 1948 to 1953, 5 primary carcinomas of the Fallopian tube were encountered. In the same period there were 791 primary malignant lesions of the female genital tract. Thus, the incidence in our material is 0.61 per cent of all female genital tract neoplasms. This figure is higher than most others reported, being double that of Hu, Taymor, and Hertig[2] and four times that of Lofgren and Dockerty.[3]

The cases here described all presented problems in exact diagnoses. In only one was the correct diagnosis suspected. The preoperative diagnosis in 3 was ovarian carcinoma and in one it was carcinoma of the body of the uterus.

The diagnosis is rarely made preoperatively, and, indeed, the presence of a malignant lesion of any kind is often not suspected. It appears significant to us that of 4 cases in this series in which preoperative cervical smears were examined, 3 were positive for cancer cells, the morphological features of which suggested adenocarcinoma. The purpose of this paper is to stress the value of the cervical smear as an aid to diagnosis of carcinoma of the Fallopian tube.

Case Reports

CASE 1.—Mrs. A. L. F. (V. G. H. No. G16281), a 57-year-old white woman, thirteen years postmenopausal, was well until Nov. 25, 1948, when she had a profuse vaginal discharge. This was brownish in color and contained some red blood. It lasted three and one-half hours. During the following two weeks she had two similar episodes.

Physical examination revealed tenderness and resistance to deep pressure in the right lower quadrant of the abdomen. There was a little serous vaginal discharge and pelvic examination showed adnexal thickening and marked tenderness in the right fornix. No definite mass was palpable.

A cervical smear had been sent to Dr. J. Ernest Ayre in Montreal, and he reported the smears to contain cells of malignant morphology scattered throughout a large amount of blood and leukocytes. From the history and the type of cell seen, he suggested the possibility of tubal carcinoma.

At operation on Dec. 30, 1948, the uterus and left tube and ovary appeared normal. The right Fallopian tube was distended, and curled on itself to the size of a large tangerine orange. This was adherent to the right broad ligament which on palpation was found to be infiltrated, making the whole right pelvic wall and broad ligament a continuous indurated mass.

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Lymph nodes presumed involved in metastatic tumor were palpable along the iliac chains, presacral region, and aorta up to the right kidney. The right Fallopian tube was removed and the condition was considered too far advanced for any further surgery.

Pathological examination revealed a retort-shaped Fallopian tube which was considerably dilated. The wall was thickened to 8 mm. and lined by soft polypoidal tumor tissue. Microscopic examination showed a fairly well-differentiated papillary adenocarcinoma (Fig. 1).

About two years after the operation she developed a bowel obstruction from intraperitoneal metastases, for which a transverse colostomy was done. Bilateral ureteral obstruction developed and her condition deteriorated rapidly and she died July 22, 1951, three years and seven months after operation.

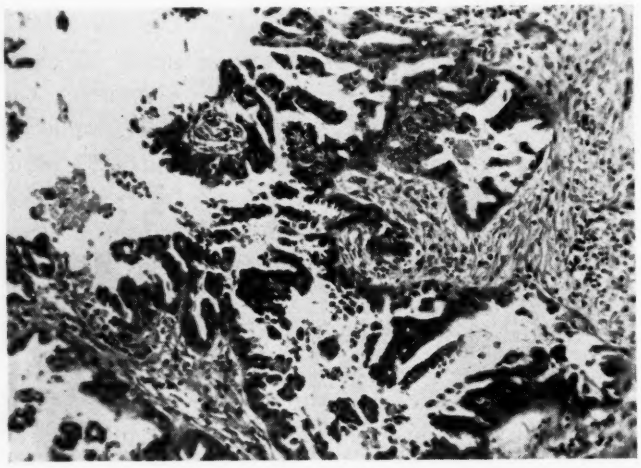

Fig. 1 (Case 1).—Section of Fallopian tube showing papillary adenocarcinoma, Grade II.

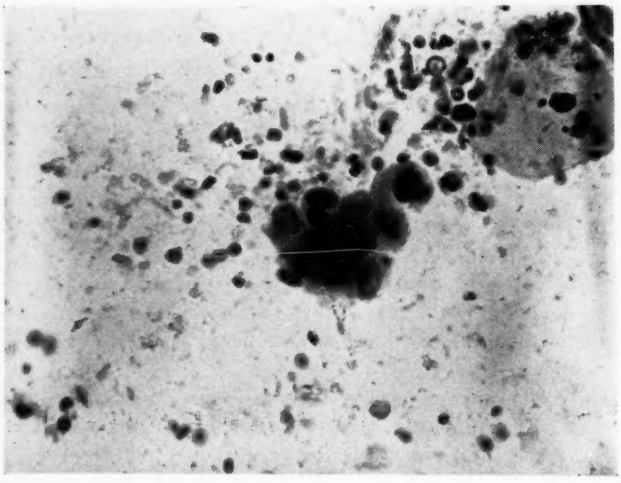

Fig. 2 (Case 2).—Cervical smear showing clumps of malignant epithelial cells.

CASE 2.—Mrs. L. H. (B. C. C. I. 39-198 [b]), a 59-year-old white woman, twelve years postmenopausal, was seen on Oct. 19, 1950. She had been in good health until two months previously when she noticed an odd sensation in the right lower side of her abdomen and a sensation of weakness in the legs. For one month she had noticed a little spotting of vaginal blood which on one occasion was a moderate flooding.

Physical examination revealed some tenderness to the right of the umbilicus and an indefinite intra-abdominal mass about 4 cm. in diameter in this region. Pelvic examination was not remarkable.

Cytological examination of cervical smears revealed the following result:

Oct. 19, 1950—Suspicious for cancer cells.

Oct. 31, 1950—Cells of definite cancer morphology present, suggesting adenocarcinoma (Fig. 2).

Dec. 5, 1950—Suspicious for cancer cells.

Repeated pelvic examination under anesthesia failed to reveal any abnormality. Uterine curettage failed to obtain any tissue for microscopic study. She continued to spot irregularly during the subsequent five months. Although a cervical smear at the end of this time was negative it was felt that the history of recurrent spotting and the previous finding of cells consistent with adenocarcinoma warranted laparotomy.

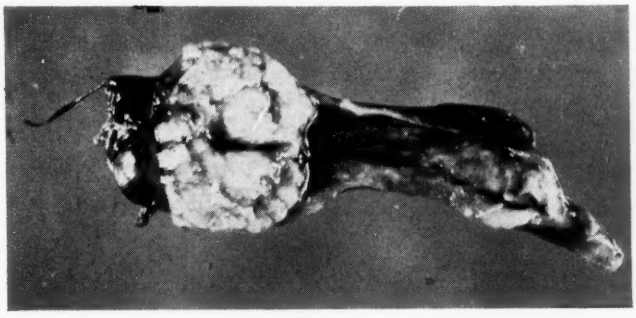

Fig. 3 (Case 2).—Fallopian tube opened longitudinally and showing papillary carcinoma in distal third.

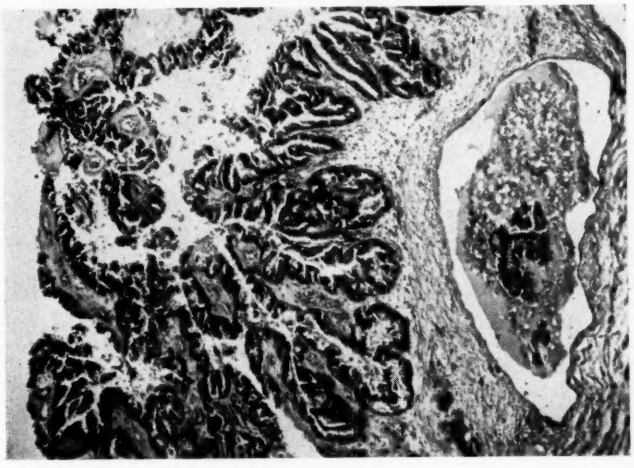

Fig. 4 (Case 2).—Papillary adenocarcinoma, Grade II, a dilated lymphatic gland containing clumps of tumor tissue.

At operation on March 28, 1951, the uterus was found to be small. There was a mild hydrosalpinx of both Fallopian tubes and these were bound down by dense fibrous adhesions. Total hysterectomy and bilateral salpingo-oophorectomy were performed.

Pathological examination showed the significant lesion confined to the left Fallopian tube (Fig. 3) which measured 8 cm. in length. The proximal portion was of uniform diameter of about 8 mm. In the distal 2.5 cm. it was dilated to 1.5 cm. in diameter and the fimbriated end was closed off. Upon opening the tube the dilated fimbriated end was found to be filled

with a papillary tumor which did not appear to have invaded the muscle wall. Microscopic examination showed a fairly well-differentiated papillary carcinom which infiltrated the wall only a short distance. A widely dilated lymphatic containing tumor tissue (Fig. 4) was found in the submucosal connective tissue.

Postoperatively the patient received deep x-ray therapy. A tumor dose of 1,980 r was given over a period of twenty days but had to be abandoned because of symptoms associated with diverticulitis of the colon. She was last seen on March 18, 1953, two years after operation and there was no evidence of recurrent disease.

CASE 3.—Mrs. M. M. (V. G. H. No. 38495), a 62-year-old white woman, twelve years postmenopausal, complained of a vaginal hemorrhage of about one cupful of blood two months previously, followed by intermittent spotting since that time. For the same period she had a constant heavy feeling in the lower abdomen with occasional sharp pains.

No cervical cytological examination was performed.

Upon physical examination she was found to have arteriosclerotic heart disease with paroxysmal auricular fibrillation. Abdominal examination revealed no abnormality. Pelvic examination under anesthesia showed the uterus to be slightly enlarged and there were bilteral masses interpreted as enlarged ovaries, that on the right being the size of an orange and the left the size of an egg. Curettage failed to produce endometrial tissue.

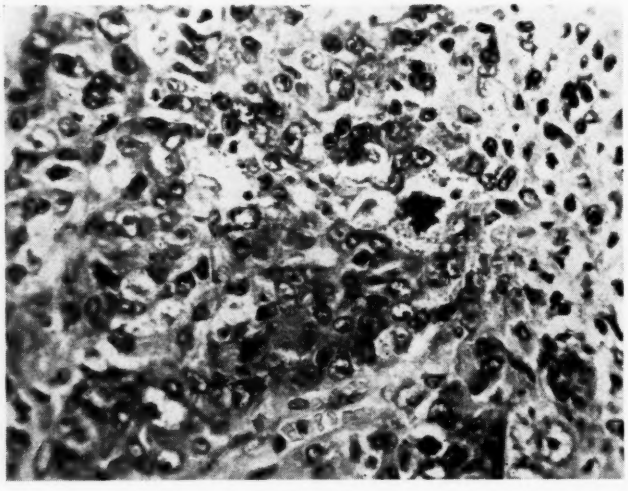

Fig. 5 (Case 3).—Section of Fallopian tube showing papillary adenocarcinoma, Grade III.

On March 28, 1951, hysterectomy and bilateral salpingo-oophorectomy were performed. At operation several small nodules interpreted as tumor implants were seen on the right pelvic wall. These were not removed.

Pathological examination showed the right Fallopian tube dilated to 3 cm. in diameter at the fimbriated end, and the lumen was filled with papillary yellowish-red neoplastic tissue. There was a leiomyoma 4 cm. in diameter in the left broad ligament and several leiomyomas measuring up to 1 cm. in diameter in the uterus. Microscopic examination of the tumor in the right Fallopian tube showed a rather poorly differentiated papillary carcinoma (Fig. 5). This had infiltrated into the muscle layers but not to the serosal surface.

Operation was followed by a course of deep x-ray therapy to the pelvis. This patient has since had several episodes of congestive heart failure, but is otherwise well two years postoperatively.

CASE 4.—Mrs. K. P. (B. C. C. I. No. 52-404), a 68-year-old white woman, was admitted to hospital March 31, 1952, complaining of difficulty in urination for one week and inability

to void for three days. For two years previous to this there had been some inconstant nocturia and dysuria. During the past one year she had lost 15 pounds in weight. There was no history of vaginal discharge.

Physical examination revealed moderately severe suprapubic tenderness. In the right lower quadrant of the abdomen was a mass which was difficult to delineate because of the tenderness. Pelvic examination was not successful because the patient was too tense. Cystoscopic examination showed marked distortion of the bladder and indicated a mass filling nearly the whole pelvis, but particularly the right side. It was considered to be a tumor of the ovary.

A cervical smear was reported negative for cancer cells.

Laparotomy was performed April 9, 1952. A large mass, bluish-gray in color, was found in the pelvis. The uterus was pushed forward. Both tubes and ovaries were found and reported as atrophic. It was impossible to find a line of cleavage in the tumor and as much as possible was scooped out and the abdomen was closed.

Pathological examination showed a mass of very soft, friable, reddish-gray tissue weighing 224 grams. Attached to this was a structure resembling a Fallopian tube 4 cm. in length and 6 mm. in diameter. This merged at one end with the tumor tissue. Microscopic sections confirmed the identity of the Fallopian tube. One section, through the distal end, showed origin of a very poorly differentiated papillary carcinoma from the mucosal lining (Fig. 6). Elsewhere the tube was surrounded by poorly differentiated carcinoma and sections through the large soft mass all showed a similar appearance.

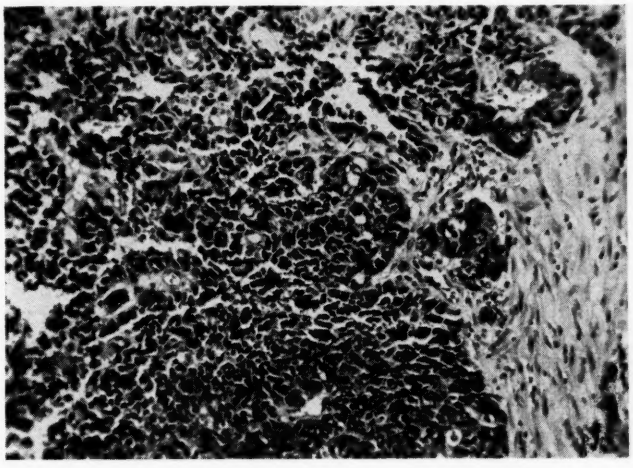

Fig. 6 (Case 4).—Section of Fallopian tube showing an undifferentiated carcinoma, Grade IV.

Postoperatively this patient received two radium insertions and deep x-ray to the pelvis, the latter constituting a tumor dose of 3,068 r given over twenty-three days.

By November, 1952, the pelvic mass had recurred. This enlarged rapidly and the patient died Dece. 24, 1953, eight months postoperatively. Postmortem examination revealed a large mass of recurrent carcinoma in the pelvis. The uterus, tubes, and ovaries were not identifiable in this tissue. Death was due to a massive pulmonary embolus, presumably from the pelvic veins. There was also complete thrombotic occlusion of the right renal artery causing infarction of the kidney. There was a left hydroureter and pyelonephritis.

CASE 5.—Mrs. A. B. (V. G. H. No. 117272), a 64-year-old white woman, nine years postmenopausal, was admitted to hospital March 18, 1953, complaining of sharp, shooting, crampy pains in the right lower quadrant of the abdomen for three weeks. These pains occurred two to three times a day and in the interval there was a dull constant pain. There was no associated nausea or vomiting. Apart from some bloody vaginal spotting on two occasions three months previously, she had been quite well.

Physical examination revealed suprapubic tenderness. There were irregular intra-abdominal mobile masses palpable between the pubis and umbilicus. On pelvic examination the uterus could not be outlined. The pelvis was filled with an indurated irregular mass, especially filling the left fornix and cul-de-sac. It was fixed and tender. An intravenous pyelogram showed a somewhat flattened bladder suggesting an extrinsic mass.

A cervical smear was reported positive for malignant cells consistent with adenocarcinoma (Fig. 7).

Laparotomy was performed on March 27, 1953. A mass was found in the pelvis at the level of the third sacral vertebra. This was attached to the rectosigmoid junction. There was also a large metastatic tumor mass in the omentum. Biopsies were taken from each of these masses and the abdomen was closed.

Pathological examination revealed a portion of thickened Fallopian tube measuring 4 cm. in length by 1.5 cm. in diameter. Upon opening this it was found to contain soft, friable, pink tumor tissue. Microscopic examination showed a poorly differentiated papillary adenocarcinoma, Grade III, originating in the mucosa of the Fallopian tube (Fig. 8). A section from the omental mass showed similar tumor tissue.

A course of deep x-ray therapy was administered to the pelvis. The patient is alive and well four months postoperatively.

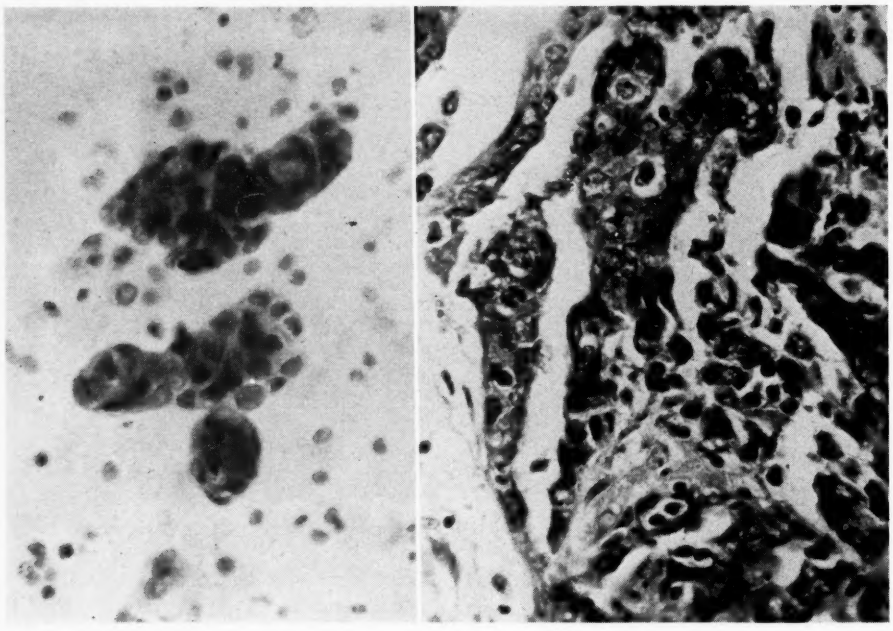

Fig. 7. Fig. 8.

Fig. 7 (Case 5).—Cervical smear showing clumps of malignant epithelial cells.
Fig. 8 (Case 5).—Section of Fallopian tube showing papillary adenocarcinoma, Grade III.

Comment

The signs and symptoms of primary carcinoma of the Fallopian tube are obscure and indefinite in the early and even in the advanced stages of the disease. Nevertheless, a common triad frequently encountered is the association of (1) bloody or serosanguineous vaginal discharge, sometimes with episodes of massive hemorrhage, (2) lower abdominal pain, and (3) presence of a pelvic mass. Most authors state these three findings in this order of frequency. If one can

exclude significant disease in the uterus by cervical biopsy and endometrial curettage, then as Martzloff[4] has pointed out, an extrauterine origin, logically tubal, and possibly malignant, may be inferred.

In view of the fact that a serosanguineous vaginal discharge, originating in the diseased tube, is the commonest complaint it is apparent that the cytological examination of this discharge should assist in arriving at a specific diagnosis. In fact, MacLean[5] urges the use of a cervical cap to facilitate collection of discharges from the upper uterine tract and refers to one case of early carcinoma of the Fallopian tube diagnosed correctly by this means. Ayre[6] suggests that screening programs in which cervical cytological examinations are done should result in earlier diagnosis of tubal carcinoma.

In the cases reported above, 4 patients complained of vaginal discharge. Cervical smears were done on 3 of these, and in each instance a positive report for cells consistent with adenocarcinoma was given. In Case 1 the diagnosis of tubal carcinoma was suggested by the cytologist. Case 4 is a false negative, but understandably so in view of the fact that there was no vaginal discharge associated with the lesion.

Except for Case 2, these are all examples of advanced carcinoma of the tube, in each instance extending beyond the confines of the tube into adjacent pelvic structures. Case 2 corresponds closely to one described by Isbell and associates,[7] which likewise was characterized by periodic vaginal bleeding over a period of six months, with no contributory findings in uterine curettage and absence of pain and pelvic mass. In our case, operation revealed a relatively small carcinoma, showing a minimum of infiltration of the tubal stroma and apparently confined to the tube. Although the prognosis would appear to be good in this case, it is significant that despite the apparently early stage and relatively good differentiation, some lymph channels, containing small clumps of tumor cells, were found in the muscle. This feature of early lymphatic involvement is probably a factor in the over-all poor prognosis in this condition. This patient has, however, survived for two years postoperatively with no evidence of recurrent disease.

The finding of malignant cells in the cervical smear under conditions described above, while pointing to a tubal origin, may, however, be significant of ovarian carcinoma or metastatic carcinoma in the pelvis from some distant primary origin. We have examined cervical smears from 20 patients in whom the diagnosis of ovarian carcinoma was eventually established. In these, 4 showed cells interpreted as suspicious and 7 showed cells of a definite malignant morphology. Whereas the cells are usually found in clumps and have the other cytological criteria[8] usually ascribed to adenocarcinoma in contradistinction to squamous-cell carcinoma as seen in cervical lesions, we have been unable to distinguish any significant cytological features that would distinguish ovarian from Fallopian tube carcinomas, or indeed from endometrial carcinoma.

Conclusions

Five cases of primary carcinoma of the Fallopian tube are described. These were seen in a five-year period and represent 0.61 per cent of 791 primary malignant lesions of the female genital tract during this period.

TABLE I

CASE	AGE	PARITY AND GRAVIDITY	BLOODY VAGINAL DISCHARGE	LOWER ABDOMINAL PAIN	PALPABLE PELVIC MASS	CERVICAL CYTOLOGY	PREOPERATIVE DIAGNOSIS	PATHOLOGICAL DIAGNOSIS	POSTOPERATIVE RADIUM OR X-RAY	FOLLOW-UP
1	57	Married	2 weeks	No	No, but adnexal thickening and resistance present	Positive	1. Hydrosalpinx 2. Carcinoma of body of uterus or Fallopian tube	Papillary adenocarcinoma, Grade II	—	Died of recurrence 2 years, 7 months postoperatively
2	59	Married Para iii Gravida iii	7 months	No	No	Positive	Carcinoma of uterus	Papillary adenocarcinoma, Grade II, with lymphatic involvement	X-ray	No evidence of disease 2 years postoperatively
3	62	Married	2 months	2 months	Yes	Not done	Bilateral ovarian carcinoma	Papillary adenocarcinoma, Grade III	X-ray	No evidence of disease 1 year, 10 months postoperatively
4	68	Married Para i Gravida i	No	1 week	Yes	Negative	Carcinoma of right ovary	Papillary adenocarcinoma, Grade IV	Radium and x-ray	Died with recurrence 8 months postoperatively
5	64	Married Para iii Gravida iii	3 months	3 weeks	Yes	Positive	Carcinoma of ovary	Papillary adenocarcinoma, Grade III, with lymphatic involvement	X-ray	Alive and well 4 months postoperatively

Examination of the cervical smear has been found of value in diagnosis, the preoperative smear being positive in 3 of the 4 cases examined, and in all 3 in which there was an associated bloody vaginal discharge.

The triad of vaginal spotting or hemorrhage, lower abdominal pain, and pelvic mass, when accompanied by positive cytology and negative cervical and endometrial biopsy, is practically diagnostic of tubal carcinoma. Carcinoma of the ovary with, or sometimes even without, tubal involvement may, however, also yield malignant cells in the cervical smear.

Grateful acknowledgment is made to Drs. G. E. Gillies, J. E. Ayre and A. E. Trites for permission to publish Case 1; Dr. A. M. Evans for Case 2; Dr. J. E. Harrison for Cases 3 and 5; and Drs. A. M. Agnew and D. B. Collison for Case 4.

References

1. Carpenter, R. J., and Jameson, W. J.: Am. J. Surg. **83**: 595, 1952.
2. Hu, C. Y., Taymor, M. L., and Hertig, A. T.: AM. J. OBST. & GYNEC. **59**: 58, 1950.
3. Lofgren, K. A., and Dockerty, M. B.: Surg., Gynec. & Obst. **82**: 199, 1946.
4. Martzloff, K.: AM. J. OBST. & GYNEC. **40**: 804, 1940.
5. MacLean, K. S.: Science **114**: 181, 1951.
6. Ayre, J. E.: Cancer Cytology of the Uterus, New York, 1951, Grune & Stratton, p. 361.
7. Isbell, P., Jewett, J. F., Allen, M. S., and Hertig, A. T.: AM. J. OBST. & GYNEC. **54**: 576, 1947.
8. Papanicolaou, G. N., and Traut, H. F.: AM. J. OBST. & GYNEC. **42**: 193, 1941.

PAPILLARY SEROUS TUMORS OF THE OVARY

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PROPER microscopic evaluation of an ovarian tumor is often a perplexing problem to even the most astute and conscientious pathologist. Accurate diagnosis is of paramount importance in formulating a prognosis and may serve as the criterion for further surgical and/or irradiation therapy. Such problems are not unique for the pathologist, but ovarian tumors offer particularly perplexing aspects. Howard Taylor[1] has aptly stated: "Ovarian carcinoma is a group of diseases and not a single one," and stressed the importance of studying particular types of tumors rather than ovarian carcinoma in general. Complete accord with this tenet has prompted our study.

Among ovarian tumors, the papillary serous group presents one of the most complex problems. Few neoplasms evoke such divergent opinions from competent pathologists. The frequent difficulty in evaluating the malignant potentialities of such lesions has motivated this histological study, in an effort to correlate features of tumor architecture with prognosis.

Previous studies have crystallized present concepts as to incidence, age, parity, symptomatology, physical signs, and associated lesions. It is well established that the minimum satisfactory operative procedure for most papillary tumors is a bilateral adnexectomy and no less than a supravaginal hysterectomy. The high incidence of tumor in the grossly normal contralateral ovary and the frequency of extension or metastasis to the fundus demand this degree of surgery.

As a basis for this study we were fortunate in having at our disposal the material collected by the Ovarian Tumor Registry* as well as the opinions of the outstanding pathologists who comprise its membership. Their notes as to the reasons for individual diagnosis were often incorporated into the reports, and were valuable in helping us formulate certain conclusions. In most instances, the Ovarian Tumor Registry diagnosis coincided with that of the authors, and the statistics herein represent the majority opinion of the members of the Registry.

Since the Ovarian Tumor Registry is young, only a short follow-up is available in many instances. We are well aware of this important shortcoming in our report. Previous studies, as well as our own, indicate the not uncommon tendency for tumors of the papillary serous group to recur late with fatal outcome, or to persist for long periods of time in a clinically well patient.

*With appreciation to the Ovarian Tumor Registry whose assistance has been invaluable in the preparation of such a paper.

Consequently, we would prefer this paper to be regarded as a preliminary study. The main value will not be apparent until re-evaluation of survivors some ten years hence is carried out. Nevertheless, enough interesting data have accumulated in the brief postoperative span of these patients to make a provisional report seem of some value.

Histogenesis

There is not complete unanimity of opinion as to the histogenesis of the serous tumor. The most commonly accepted theory suggests an origin from the germinal epithelium of the ovary. At times it is possible to observe in the sections from such a tumor all transitions from early invagination of the surface epithelium with tiny papillary excrescences, through the formation of simple inclusion cysts, to the development of a definite papillary serous cystadenoma. (This is well depicted in Fig. 383 in Novak's[5] textbook on pathology.) This germinal epithelium is characteristically quite variable in appearance. The most prevalent cells are of the simple cuboidal type; however, ciliated, columnar, and even secretory varieties are not uncommonly seen. Since the surface epithelium of the ovary is embryologically a derivative of mesothelium, the potentialities as to cell type are almost unlimited.

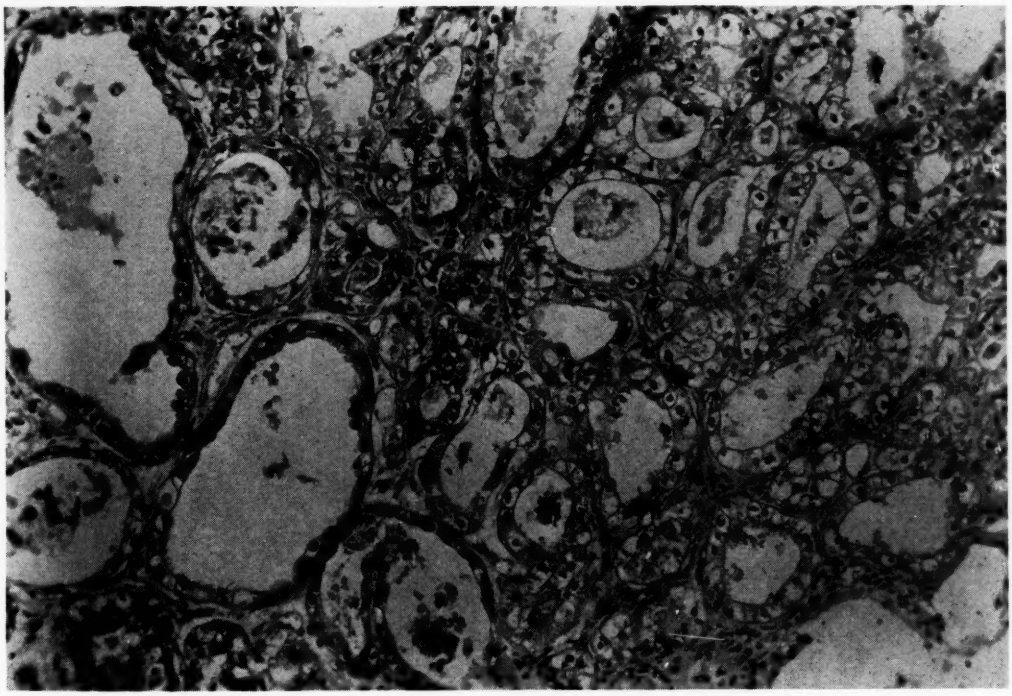


Fig. 1 (OTR 339).—Tubular pattern lined by typical clear cells. Some areas showed more solid nests while others were more suggestive of mesonephroma with tufting (see left midportion). Many characteristically papillary serous tumors showed these variations in different areas and lend support to an origin from both germinal epithelium and Wolffian duct remnants.

Gemma Barzilai[2] has suggested that the serous tumors arise from a tubal type of epithelium, and prefers to classify them as "endosalpingiomas." It is undeniable that cells of both the secretory and ciliated varieties are com-

monly found in individual neoplasms of this group. In addition, certain papillary tumors of the ovary are morphologically indistinguishable from tubal carcinoma which is characteristically extremely papillary. These histologic similarities, however, fit only a relatively small proportion of this rather large group.

Remnants of the mesonephric system are common findings in the region of the ovary. Such structures as the rete ovarii, the epoophoron and paroophoron, and the Wolffian duct are noted in a large majority of routine sections from this area. Furthermore, the epithelium of these structures is recognized to vary tremendously, and certain tumors (mesonephromas) have been described as probably arising from such embryonic residua. The parovarian cyst, originating in Wolffian duct tissue, may on occasions produce a papillary pattern indistinguishable from the typical papillary serous cyst.

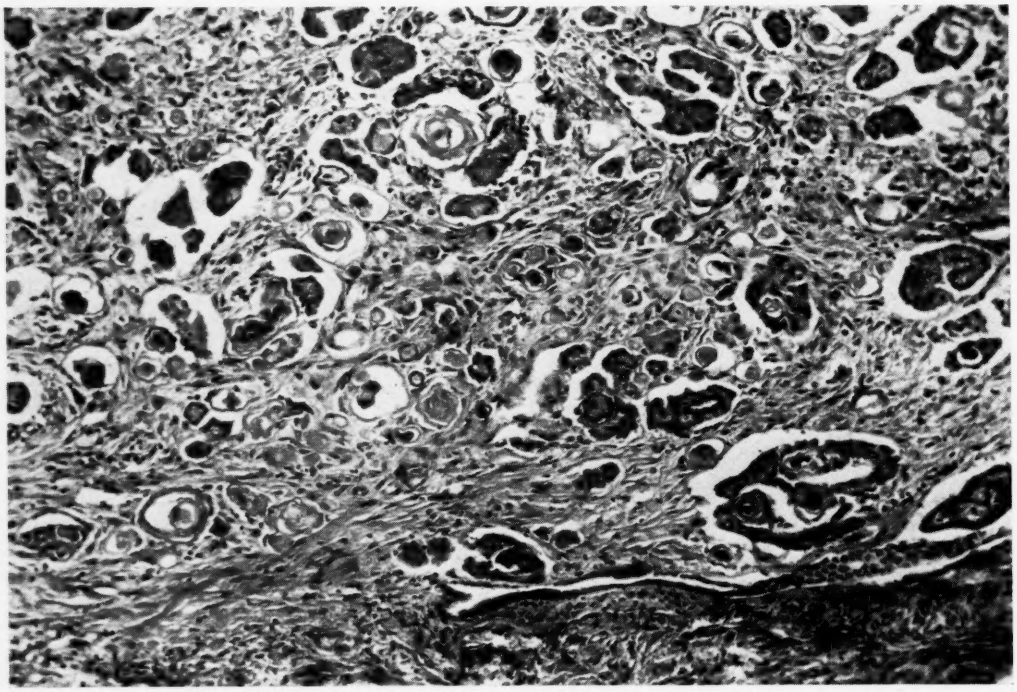
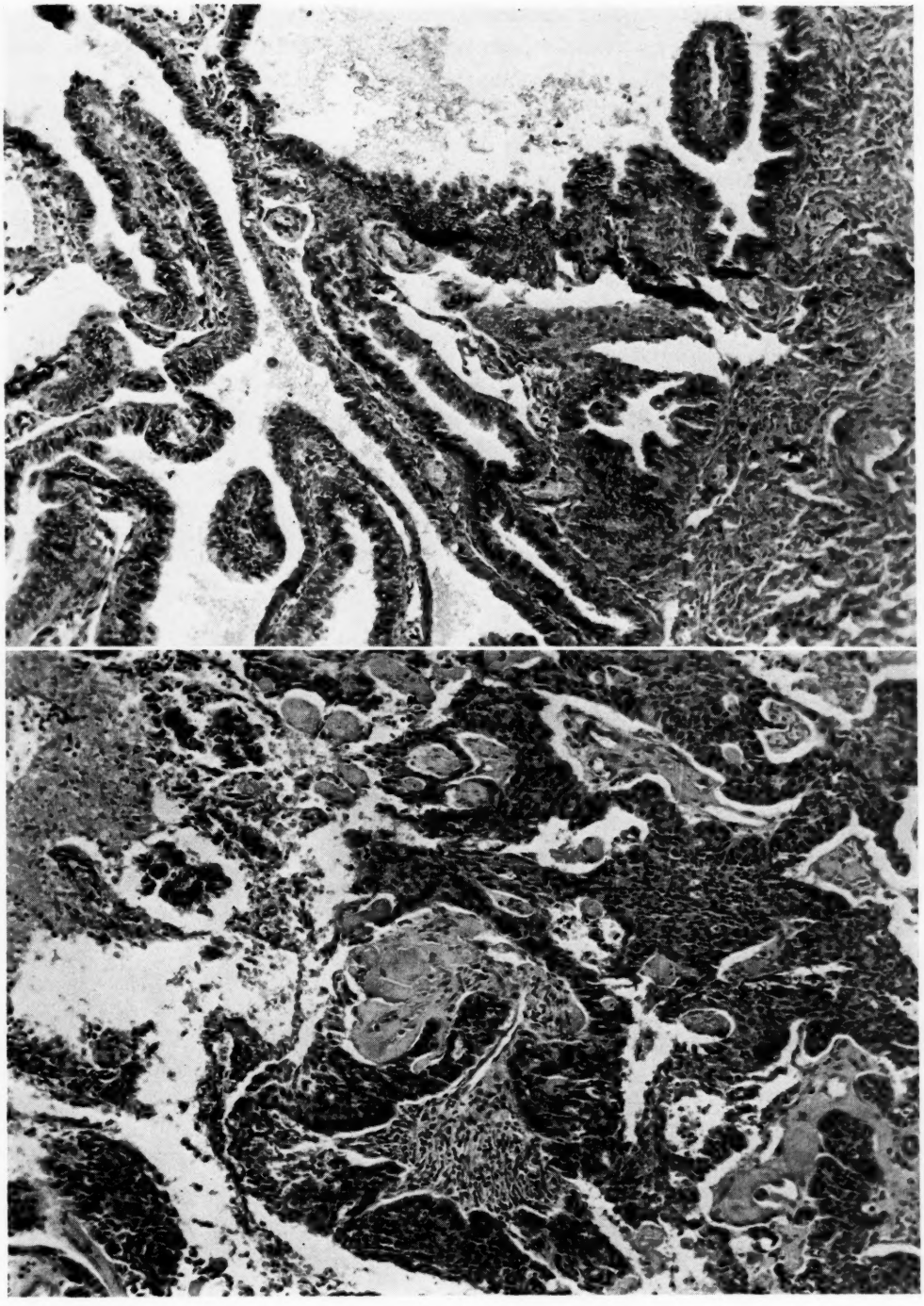


Fig. 2 (OTR 112).—Psammoma bodies replacing papillae in an implanting serous tumor of low-grade malignancy. These inclusions are almost pathognomonic of serous growths.

In view of these multiple histogenetic possibilities, it is rather difficult to attempt to lay down hard and fast criteria as to the origin of each individual tumor. It is not rare to find the same tumor presenting areas representative of the typical papillary serous group adjacent to those which fit the presently accepted criteria for mesonephroma. "Clear-cell" adenocarcinoma and serous cystadenocarcinoma have been found to coexist not uncommonly (Fig. 1, OTR 339).

Nevertheless, an attempt to evaluate the various concepts of the histogenesis of these tumors has been one of our main points of study. It seems

A.



B.

Fig. 3 (OTR 346).—*A*, Is representative of most of the tumor showing normal epithelial lining without proliferation or anaplasia. The cystadenoma should be regarded as benign on the basis of this section.

B, Shows one block of the tumor revealing a rather marked malignant pattern. This should emphasize the importance of multiple microscopic sections.

likely that the great majority arise from the germinal epithelium since the stages of development can be demonstrated clearly by histological sections of the same tumor. Comparison of benign surface papillomas with those seen in the simple papillary cystadenomas prove them to be identical. Invaginations of surface epithelium can be seen adjacent to tiny cystic structures and the epithelium can be superimposed if serial sections are made. In cases demonstrating numbers of these simple inclusions, the psammoma bodies, so frequently seen with serous tumors, are also common (Fig. 2, OTR 112). Furthermore, the usual variations in the epithelium of the tumors are similar to the differences noted in the normal germinal epithelium.

Nevertheless, certain tumors may exhibit such variation as to imply that both germinal epithelium and adjacent mesonephric elements may be simultaneously stimulatd to tumor formation. Such a situation would explain the totally dissimilar cell pattern occasionally seen in adjacent areas of the same tumor and the frequent association of clear-cell carcinoma and mesonephroma with a typical papillary serous tumor. In view, however, of the common ancestry of germinal, Müllerian, and mesonephric epithelium, the argument as to the histogenesis of each individual tumor may be merely an academic one.

The extreme variation in cellular detail exhibited by many of these serous tumors makes prognosis a well-nigh impossible task. It is the rule, rather than the exception, to find different degrees of activity in adjacent microscopic fields. Unquestionably malignant changes can be found in one area, whereas the remaining sections of the same tumor may represent definitely benign patterns (Fig. 3, A and B, OTR 346). Such incongruities often coexist in the same tumor or even in the same microscopic field. The frequent finding of this variation in different areas makes the study of many blocks imperative. Certainly it would be foolhardy to offer an accurate diagnosis and prognosis on the basis of one section of a papillary serous tumor. Of equal importance is a description of the operative findings and gross specimen. The presence of papillary excrescences, ascites, and microscopic extension or implantation may coexist with a microscopically benign tumor. Such "benign" tumors may kill by the local effects of their implants with continued formation of ascites, infection, and eventual debility and cachexia.

Criteria for Histological Interpretation

The Ovarian Tumor Registry classification of the papillary serous tumors divides the group into benign, malignant, and potentially malignant tumors. In most cases, no difficulty is encountered in arriving at an accurate diagnosis and prognosis in the first two classes. The third group, however, commonly offers tremendous problems.

We have attempted to set up certain criteria which can be employed in evaluating the malignant potentialities of these tumors. Although no hard and fast rules can be established, the following features seem to be of major importance:

1. Proliferation of Epithelium.—The simple papillary tumors are lined by a single layer of epithelium with minimal proliferative tendencies. Advanced degrees of this characteristic have an ominous significance and strongly suggest malignant tendencies. However, one must be ever mindful of tangential section, which can produce the picture of a "piled-up" epithelium, but any epithelium of more than 3 to 4 cell-layer thickness is frankly suspicious.

2. Adenomatous Patterns.—These are quite compatible with benignity. Indeed, such an appearance can be produced by numerous germinal inclusions in the region of the primary cystic tumor. Markedly adenomatous changes, however, are often associated with such features as epithelial proliferation and papillary tendencies. Since these variables are so commonly coexistent, an increased adenomatous pattern is at least circumstantial evidence of a malignant trend and other criteria should be carefully searched for.

3. Anaplasia and Neoplasia.—The usual standards for distinguishing benign from malignant tumors must be applied. It is important to realize that, as previously noted, considerable variation in cell type is frequently present in the lining epithelium. As far as can be determined, the presence of such variation cannot be interpreted as evidence of a malignant tendency, although advanced degrees of undifferentiation should be regarded as ominous. Infection can lead to considerable abnormality in the microscopic pattern with the production of a pseudomalignant appearance, and this factor must be given proper evaluation.

Degenerative changes are also common; especially in the large proliferative tumors. A lining epithelium may be so distorted by accumulated secretion as to mimic real anaplasia. Vacuolization, nuclear clumping, hyperchromatosis, etc., can likewise lend confusion to an already confused pattern.

4. Stromal Invasion.—The lining epithelium of papillary tumors does not normally encroach on the contained stroma. As increased epithelial proliferation occurs, extension into the stroma may take place and significant degrees of this should be regarded with suspicion. Indeed, if one can be certain of real stromal invasion, this is quite definite evidence of a malignant nature.

5. Extension to Adjacent Structures.—When a histologically benign tumor extends into the adjacent broad ligament, tube, omentum, and adjacent structures, the prognosis must be guarded. Just as there is a locally invasive hydatidiform mole (in contrast to the widely extensive and malignant chorionepithelioma) so we feel that certain papillary serous tumors show rather marked but local invasive tendencies. They are prone, not to distant dissemination, but to infiltration into neighboring tissues. Incomplete removal (and on occasion complete removal may be technically difficult) may lead to recurrent tumor masses rather than a widespread abdominal implantation. Patients may live with such recurrences for years.

6. Papillae.—As a general rule, the more papillary the external surface of these serous cysts is, the greater the malignant potentialities. Obviously, this feature must be taken in conjunction with other factors (1-5). Certainly, an extensive externally papillary picture has a more serious connotation than

if the papillae are internal unless the cyst is ruptured at operation; under these circumstances there is probably little difference. Sometimes the proliferative tendency is so marked as to exhibit multiple tiny papillae, looking not unlike "syncytial buds," and this property is suggestive of an active lesion (Fig. 4, OTR 566). As the papillary pattern becomes increasingly complex, internally or externally, more solid areas may develop, and this should generally be regarded as an extremely adverse sign.

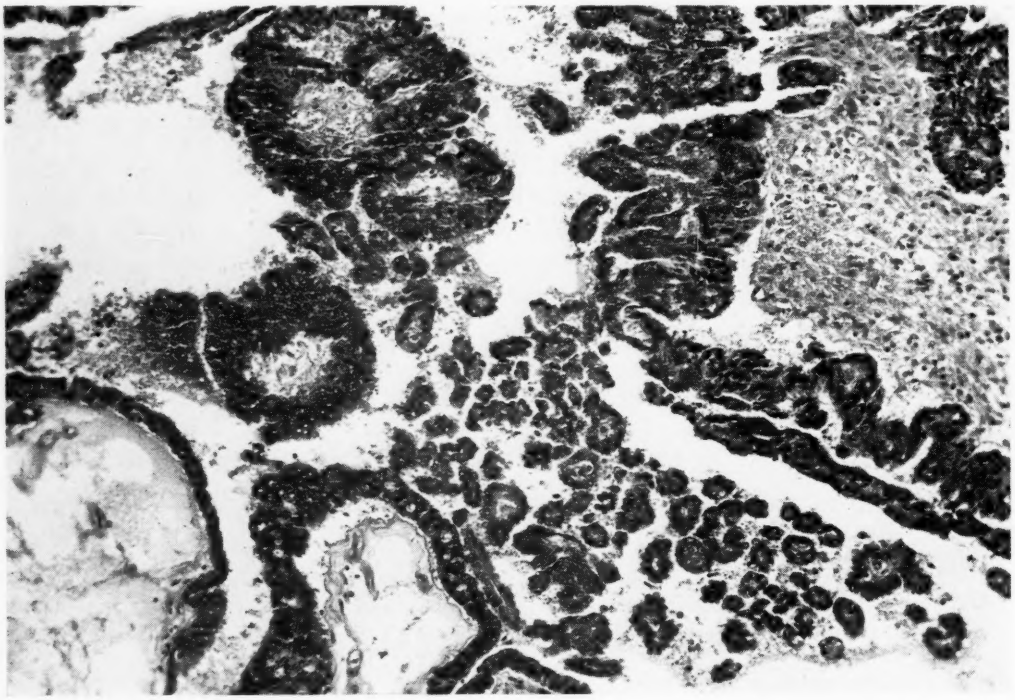


Fig. 4 (OTR 566).—Note the extreme degree of papilla formation with multiple tiny buds. Cellular proliferation and anaplasia are also present. This type of lesion has marked implanting and infiltrative tendencies and, although not prone to distant metastasis, may prove fatal.

Tumor Groups

Benign.—There were 25 cases in which a diagnosis of benign papillary serous cystadenoma was made by the members of the Ovarian Tumor Registry, and in whom a three- to ten-year follow-up was available. Only one of this group showed further evidence of tumor. In this patient a unilateral salpingo-oophorectomy was performed for a papillary cystadenoma which was removed incompletely due to technical difficulties. Five years later a recurrence was noted in the region of the previous operative procedure. Complete surgery of the remaining pelvic viscera was then carried out and the recurrence and remaining pelvic viscera were removed. The patient shows no residual tumor two years later.

Of these 25 patients, who ranged in age from 23 to 70 years, unilateral operation was done in 40 per cent, predominantly in the younger age group, and several uneventful pregnancies ensued. Ascites was infrequent, being noted

in only two instances, despite the papillary nature of many of these lesions. Some of the tumors were very large (up to the xiphoid) and often bilateral, but our data are not complete enough to give exact statistics.

In most instances, all of the specimens were rather obviously histologically benign, and there was complete unanimity of opinion among all of the pathologists in so far as diagnosis was concerned.

In applying the previously suggested criteria to this benign group, it was found that evidences of cellular anaplasia were almost uniformly absent and that trends suggestive of malignancy were minimal.

Malignant.—Forty-seven cases of papillary serous cystadenocarcinoma were diagnosed and the end results, along with surgical treatment, are tabulated in Tables I and II. We made no particular attempt to subdivide these tumors into grades of malignancy as was done by Munnell and Taylor. In our opinion, it is quite apparent that the cellular activity of the tumor closely parallels the clinical course, but evidence of extension of the tumor is also of major importance in formulating an accurate prognosis.

TABLE I. SALVAGE (ALL GROUPS)

	BENIGN	POTENTIALLY MALIGNANT	MALIGNANT
Alive for Years Following Treatment.—			
1		1 questionable prognosis	
3	10	6	4
5	5	5	4
7	7	2	3
	22	14	11
Alive With Recurrence.—			
1			
3			1
5	1	1	2
7			2
	1	1	5
Dead.—			
1	1 (not of tumor)	1	24
3	1 (not of tumor)	1	4
5			2
7			1
	2	2	31
Total	25	17	47

TABLE II. RESULTS WITH DIFFERENT PROCEDURES ON *Malignant* TUMORS

	DEAD			ALIVE		
YEARS POSTOPERATIVE	1	3	5	1	3	5
Hyterectomy and bilateral salpingo-oophorectomy	16	3	1		3	9
Incomplete	6				2	1
Biopsy only	3	2				1
Total	25	5	1		5	11

A rather active but localized tumor may be cured (Fig. 5, OTR 568). Conversely, a patient with an extensive tumor of low-grade activity may live for

a long period of time with minimal treatment. Such a case is Ovarian Tumor Registry Case No. 576 (Fig. 6); an exploratory operation was performed in 1940 and declared the tumor inoperable although biopsies were taken. X-ray therapy was given. In 1942 she was again explored and simply biopsied (as previously). In 1948 she came to Johns Hopkins Hospital and had a supravaginal hysterectomy and bilateral salpingo-oophorectomy. The sections showed a low-grade malignancy but, when she died six months later, distant metastases showed more activity. In other words, this is an eight-year salvage of a patient with inoperable carcinoma whose original therapy consisted of only biopsy and x-ray.

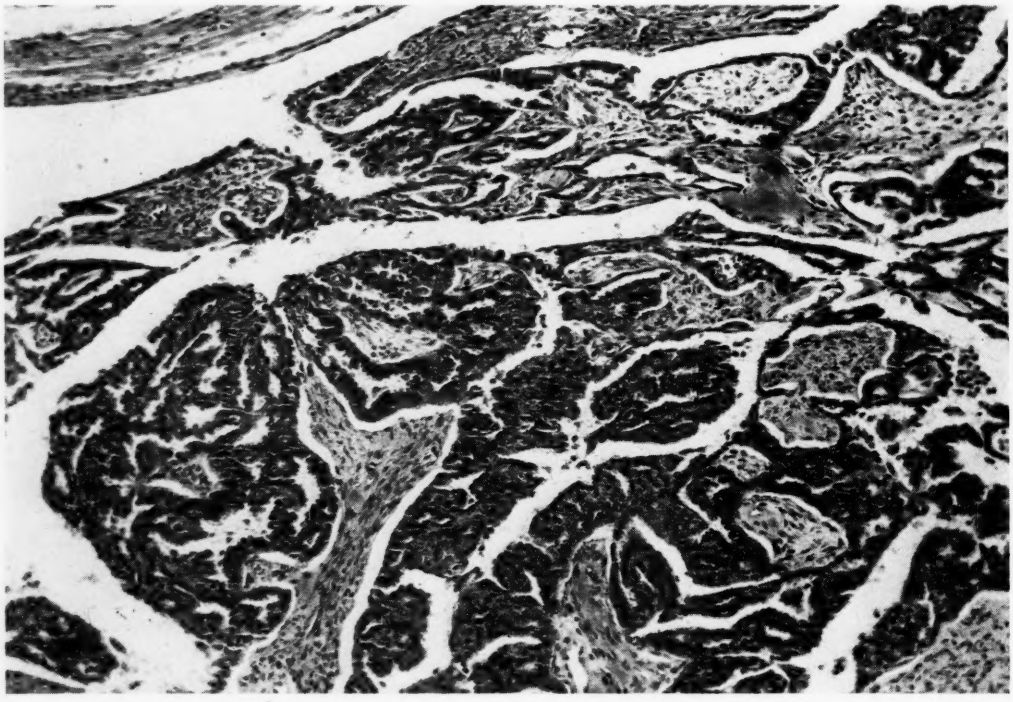


Fig. 5 (OTR 568).—Patient alive and well seven years despite the active tumor shown above. Although the growth seemed confined to one ovary, complete operation revealed tumor in the contralateral ovary (probably retrograde lymphatic spread).

Of the 47 patients diagnosed as having malignant tumors, 31 are now dead, 5 are living but with evidence of recurrence, and 11 are living and well for varying lengths of time as may be noted in Table I. It is at once apparent from this table that the majority of deaths occur within a year or two of operation, and a large proportion of these patients had extensive advanced tumor so that complete removal was impossible. Several patients, however, with clinically rather advanced tumors, ascites, and implants did not die until five to seven years following surgery.

Five patients are still alive but with recurrence up to seven years postoperatively. A review of the histological sections in these patients with late recurrence or with a prolonged survival following obviously incomplete

surgery reveals that without exception the tumors were of only moderate degrees of activity. They were often very papillary, associated with implants and ascites, but there was never the extreme degree of a solid, very malignant-appearing tumor. Cellular proliferation was never marked, anaplasia never extreme, and often cell detail was good. It would seem that this particular group of malignant tumors is capable of allowing the patient a rather long and productive life even if complete cure is not obtained.

Clinically it was of interest that the majority of this group of patients had received deep x-ray therapy. We concur with previous impressions that this is a very worth-while adjunct to surgery in the papillary carcinomas of low-grade activity. In the more active, solid, cystadenocarcinomas, it seemed of only limited value and not worth the bother or expense.

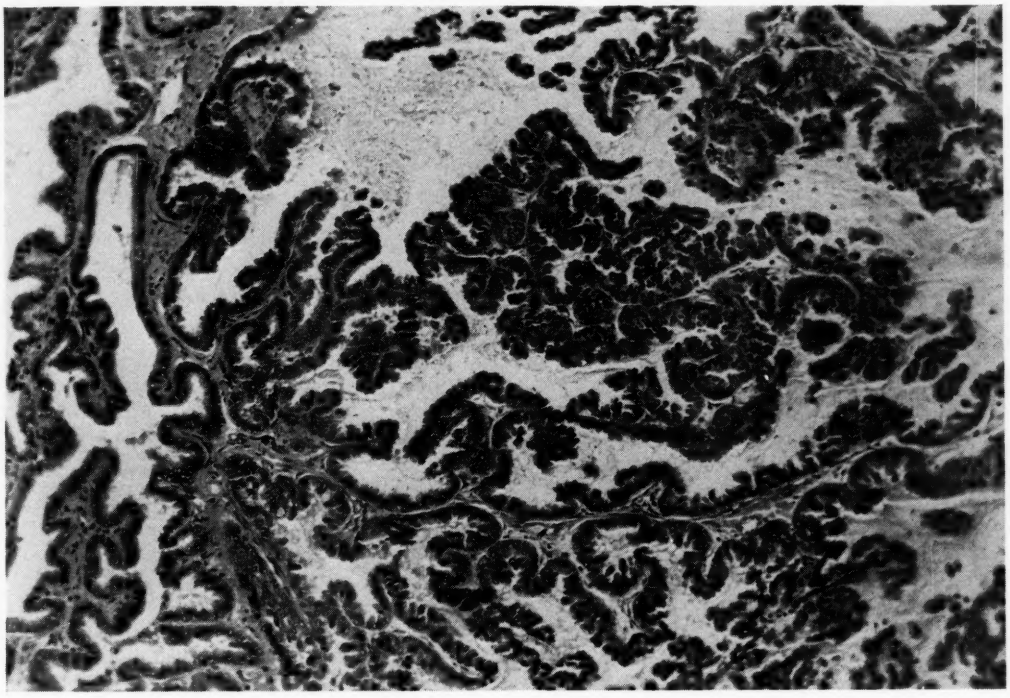


Fig. 6 (OTR 576).—Biopsy taken in 1942. Only x-ray given because patient had widespread technically inoperable lesion. Five years later the same histological pattern was present. Tumor quite papillary, but no extreme malignant trends.

Diagnosis of malignancy in the more advanced tumors was rarely a problem, and there was almost complete concurrence among the Ovarian Tumor Registry members. In the less active papillary tumors, the problem becomes more complex, and it was not rare to see divergent opinions.

Potentially Malignant.—This smaller group of 17 represent the real problem to the gynecological pathologist, and many of the less active malignant tumors mentioned in the preceding paragraph were listed thus by one or two of the five members of the Ovarian Tumor Registry.

TABLE III. OPERATIVE PROCEDURES (ALL GROUPS)

TYPE OF OPERATION	BENIGN	POTENTIALLY MALIGNANT	MALIGNANT
Hysterectomy and bilateral salpingo-oophorectomy	15	8	32
Incomplete	10	9	9
Biopsy only	0	0	6
Total	25	17	47

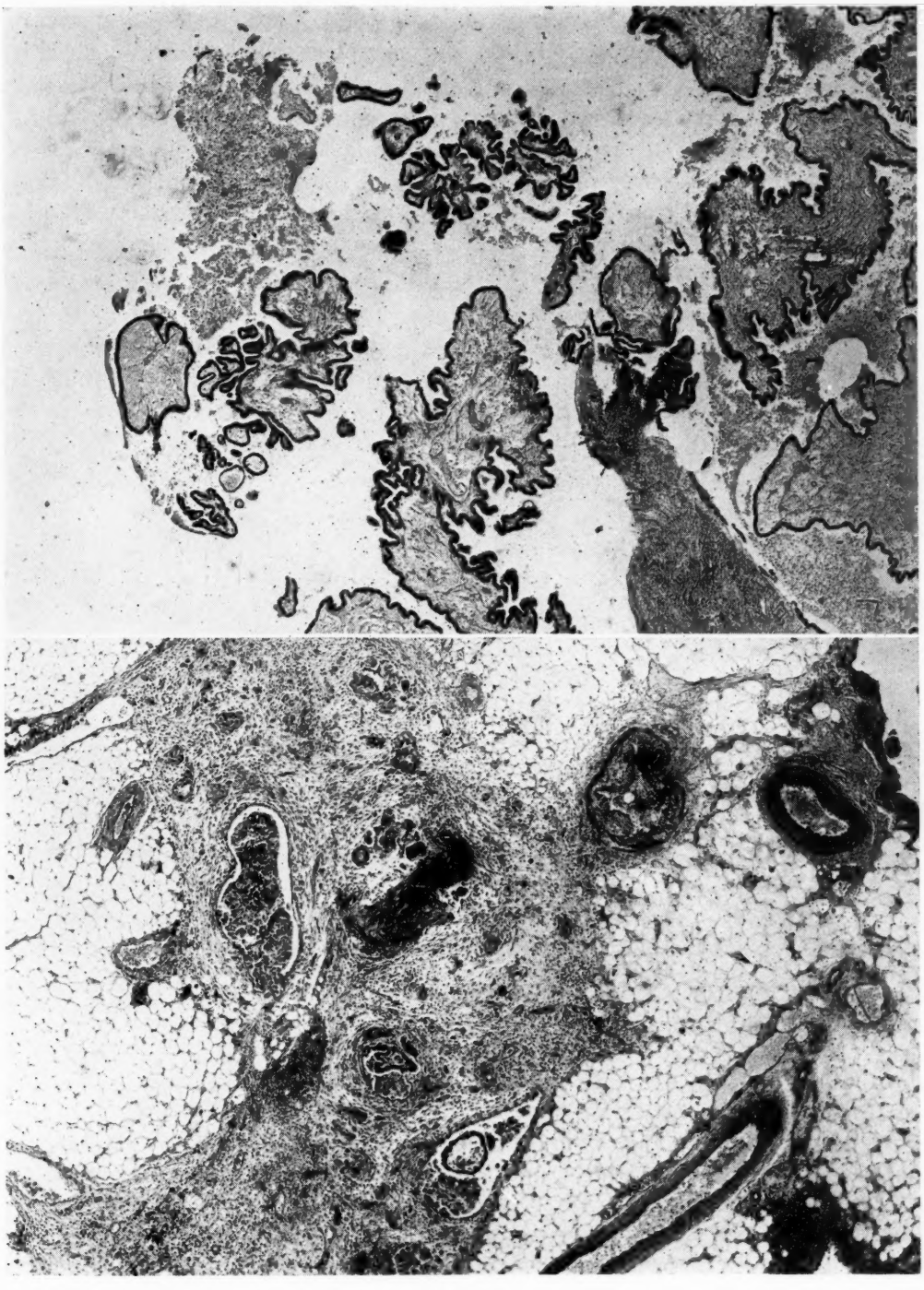
Certainly it seems that some papillary serous cystadenocarcinomas may start as a very malignant growth. In others there appears to be a transaction from a benign to a malignant tumor. At just what point does that intangible change take place, and what will enable us to recognize that ill-defined but all-important line of demarcation?

Fig. 7 (OTR 162).—Note predominance of small papillae with proliferative abnormal pale-staining epithelial lining. "Implanting tendency" suggested by loose clumps of viable-appearing cells in upper midportion.

Study of this small group of 17 patients was helpful to us, but not all revealing. Two of the patients died within three years of their operation. Both had removal of both adnexa without hysterectomy. A third patient had a recurrence four years after a unilateral salpingo-oophorectomy at which time there was gross spillage. Table III shows the operative procedures for this and other groups.

One of the patients who died (two years postoperatively) had a tumor that was microscopically of only moderate histological activity, but was very large, papillary, and associated with ascites and implants (Fig. 7, OTR 162). The second death, six months postoperatively, was caused by a rather innocuous-

A.



B.

Fig. 8 (OTR 495).—*A*, Shows very innocuous-appearing tumor with minimal papillary formation, proliferation, or neoplasia.

B, Shows extraovarian extension into vessels and fat. Again the importance of multiple sections and gross description is emphasized.

appearing but extensive infiltrating tumor (Fig. 8, OTR 495). The recurrence (Fig. 9, OTR 384) occurred in a patient whose externally smooth-walled cyst was ruptured at operation four years before.

The remaining 14 patients are alive and well after varying types of operation (Table I). At least two of these were noted as having ascites and implants at operation, but are still alive, eight and five years later, respectively. Both had a subtotal hysterectomy and bilateral salpingo-oophorectomy. From this, we may deduce that complete removal of the parent tumor may on occasion be followed by rather remarkable regression of the peritoneal implants, although permanent cure is not always achieved.

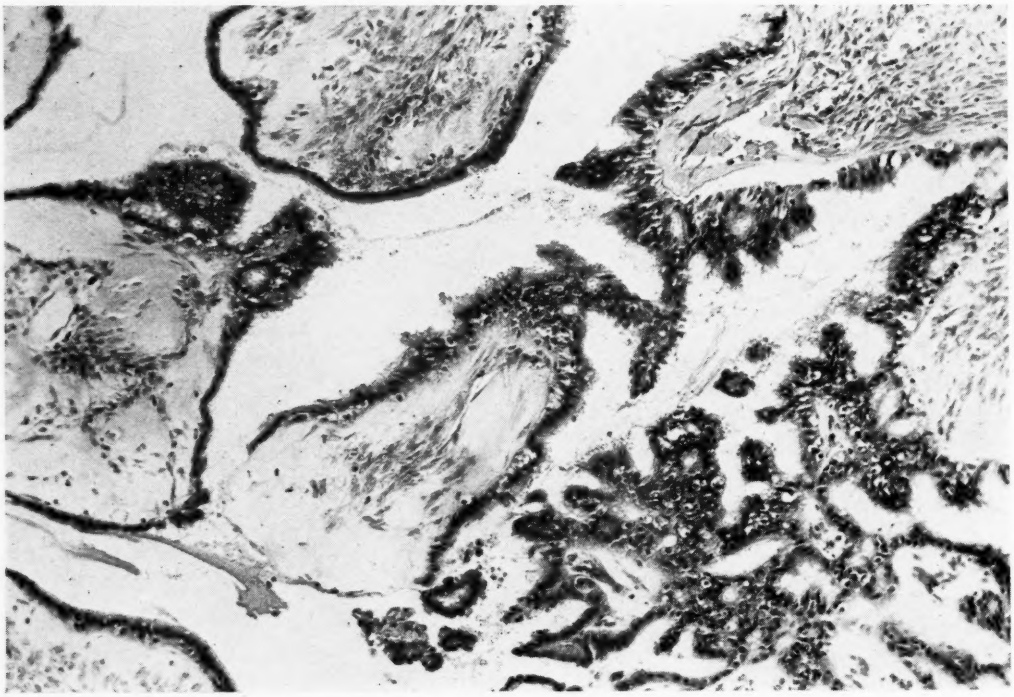


Fig. 9 (OTR 384).—On the basis of this representative section, one would be inclined to consider this a benign tumor. There is minimal activity, but recurrence followed spillage at simple operation.

Comment

We feel rather strongly that no one can predict the final outcome of a given papillary serous tumor of the borderline variety. Certainly no pathologist should be asked for a prognosis without the benefit of many representative sections, and an accurate detailed description of the gross specimen. The presence of external papillae on the cyst wall, the finding of implants or ascites, evidence of local extension, and other details should be noted. Even with this material, there are tumors on which an opinion may be given but a prognosis withheld.

The histological criteria for diagnosis have been listed previously. Of particular importance in this "potentially malignant" group was the heaping

up of the lining epithelium to more than several cell layers with the formation of solid buds. This tufting is suggestive of malignant tendencies, and along with it one can often observe a departure from normal differentiation. Wherever histological evidence of spread to tube, mesosalpinx, peritoneum, etc., could be found, the outlook is unfavorable.

It appears likely that in addition to the outright benign and malignant papillary tumors, one must recognize as a distinct and clinically different entity the potentially malignant or "implanting" variety of tumor. It rarely metastasizes, but is prone to extend by simple dissemination of exfoliated papillae (a sort of seeding to the peritoneal surfaces in the pelvis) or by local extension to adjacent viscera. This lesion may be thought of as analogous to stromatosis, invasive mole, and other low-grade malignancies, which may be compatible with a long life although the tumor may not have been eradicated, and a five-year salvage does not imply permanent cure.

These cystadenomas are generally excessively papillary with multiple tiny buds of epithelial cells and little or no evidence of proliferation or anaplasia. Often there is gross or microscopic evidence of extension or peritoneal implants, but these need not always be demonstrated. On occasion the tumor seems grossly to be confined to the ovary, but an extensively papillary nature especially in association with small clumps of viable-appearing epithelial cells should lead to a guarded prognosis (Figs. 4 and 7). It should be emphasized that this type of cystadenoma may appear perfectly innocuous from a histological standpoint but may run a protracted and inevitable fatal course.

No one feature of an ovarian serous tumor should be regarded as diagnostic; all must be considered together, gross and microscopic. When faced with the problem at the operating table, the surgeon should generally treat the patient with a papillary tumor in a radical fashion; conservative operation should be considered only as a calculated risk in the young childless woman. Frozen sections are of minimal benefit in this type of tumor; inspection and excision of the removed cyst will be of greater aid to the pathologically minded and trained gynecologist, and should be mandatory in the young patient in whom a unilateral adnexectomy is contemplated.

A final word of caution seems advisable. In cases which are equivocal in the operating room, the wise surgeon will err on the conservative side. One can always complete an incomplete operation a week or so later, but he cannot replace the removed uterus or adnexa in a woman who desires further pregnancies.

Conclusions

1. Eighty-nine cases of papillary serous tumors of the ovary from the files of the Ovarian Tumor Registry are reviewed.

2. Histogenesis is discussed and reasons for the acceptance of germinal epithelial origin as the most likely theory are presented.

3. Various criteria for the determination of malignancy in the individual tumor are suggested with the common histologic and technical errors.

4. The intermediate group of potentially malignant or implanting tumors presents the most complex problems as to prognosis, and the vagaries of this group are discussed.

5. Salvage of the benign, malignant, and potentially malignant tumors is presented with full appreciation of the inadequacy of the follow-up.

References

1. Munnell, E. W., and Taylor, H. C., Jr.: Am. J. Obst. & Gynec. **58**: 943, 1949.
2. Barzilai, Gemma: Atlas of Ovarian Tumors, New York, 1943, Grune and Stratton.
3. Javert, Carl T.: S. Clin. North America **33**: 557, 1953.
4. Allan, M. S., and Hertig, A. T.: Am. J. Obst. & Gynec. **58**: 640, 1949.
5. Novak, Emil: Gynecologic and Obstetric Pathology, Philadelphia, 1952, W. B. Saunders Company.

CARCINOMA OF THE OVARY ARISING FROM AN ENDOMETRIAL CYST

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CARCINOMA of the endometrium and endometriosis are encountered quite frequently as individual pathological entities. However, the origin of a carcinoma from an endometrial cyst of the ovary is a most unusual occurrence. To date, a total of 26 cases have been reported in which it was presumed that cancer had arisen in endometrial tissue in the ovary. Of these, only 12 have been accepted as conclusive by most authorities.

In 1925, Sampson[1, 2] published an extensive study in which he described 7 cases. He listed the strict criteria necessary to prove that endometrial tissue had become malignant:

1. "The actual demonstration of both cancer and benign endometrial tissue in the same ovary."

2. "The cancer and benign endometrial tissue must bear the same relation to each other that cancer of the body of the uterus bears to the nonmalignant portions of the endometrium."

3. "It must be shown that the cancer arose in this tissue and that it is not invading it from some other source."

Sampson concluded that, in 4 of the cases, the carcinoma could be considered as having developed in the epithelial lining of a benign cyst of endometrial origin. In the other 3 he was convinced that the carcinoma had arisen in ovarian endometrial tissue which had not developed into an endometrial cyst.

R. Meyer[3] made a careful study of Sampson's cases, and, like Corner, Hu, and Hertig,[4] questioned whether more than one of Sampson's cases fulfilled his own requirements. The latter authors described 3 cases in which they thought that it was highly probable (though not certain) that the cancer had arisen from endometrial tissue. One year previous to this report, Allan and Hertig[5] reviewed a series of 265 ovarian tumors. In 3 of these, they were convinced that carcinoma had arisen in pre-existing endometriosis.

Scott and Te Linde[6] concluded that endometrial tissue in an ovary could develop into a malignant tumor.

Teilum[7] described a case of a typical endometrial cyst in which the histological picture showed a transition from endometrial epithelium into a malignant growth. Kuzma[8] reported two cases in which adenoacanthoma and ovarian endometriosis were associated. In one case, he was certain that there was a causal relationship between the two; in the other, the histological picture was not so convincing.

In 1947, Rauramo[9] recorded a case in a 52-year-old woman at the menopause, which seemed to prove that the epithelium of typical endometriosis can undergo malignant degeneration in the same manner as the glandular epithelium of the corpus uteri. In the same year, Miller and his co-authors[10] reported the case of a 42-year-old woman in which adenocarcinoma had arisen in an endometrial cyst of the ovary.

Fig. 1.

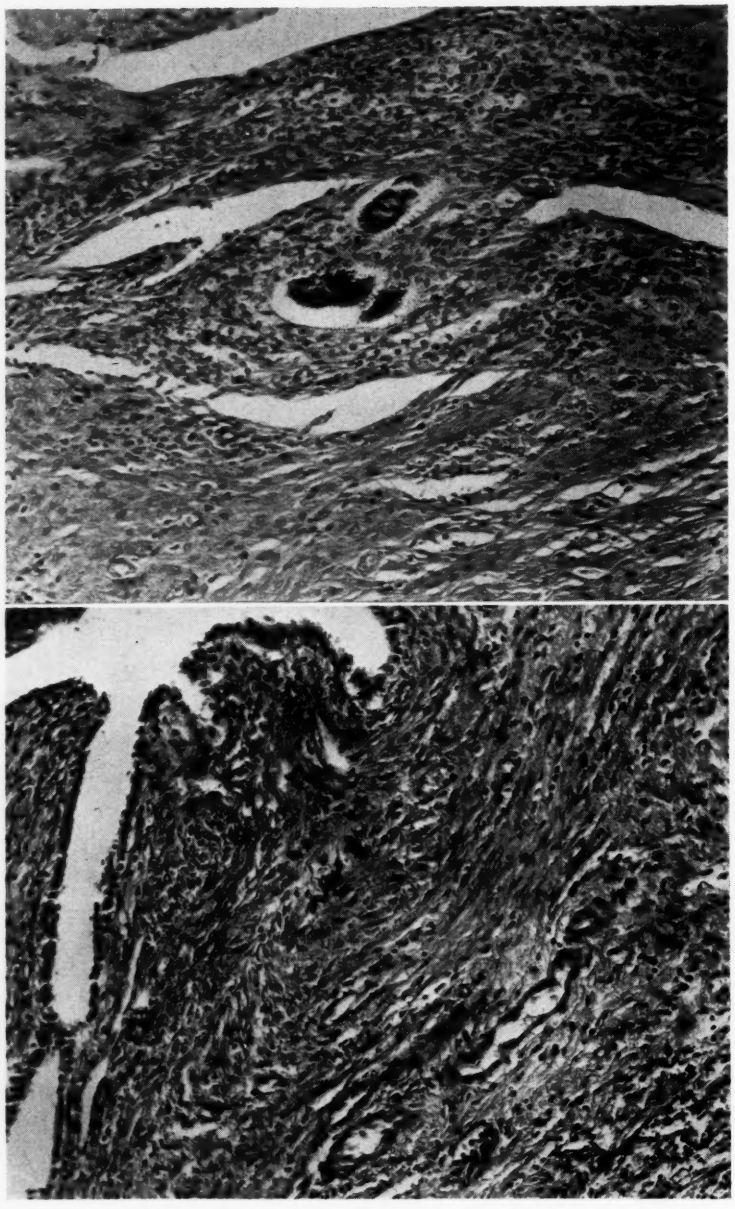

Fig. 2.

Fig. 1.—Case 1. Section demonstrating endometrial implants in the ovary.
Fig. 2.—Case 1. Section demonstrating endometriosis of the ovary.

Fredrikson[11] in a series of 181 cases of endometriosis found 3 cases in which endometriosis and a malignant tumor of the ovary occurred simultaneously. In one case, that of a 50-year-old para i, gravida i, bilateral ovarian carcinoma was present with solid adenomatous and cystic papillary structures. Also in the histological picture were endometrial cysts. The cancerous areas

Fig. 3.

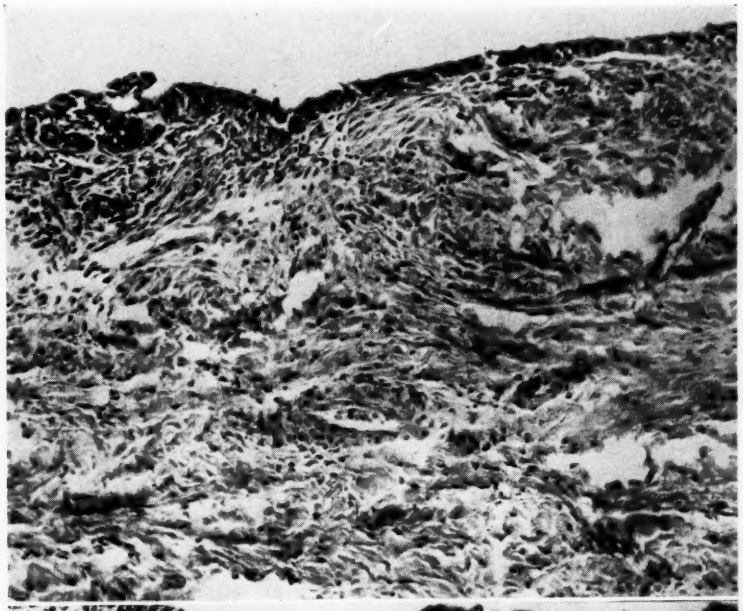

Fig. 4.

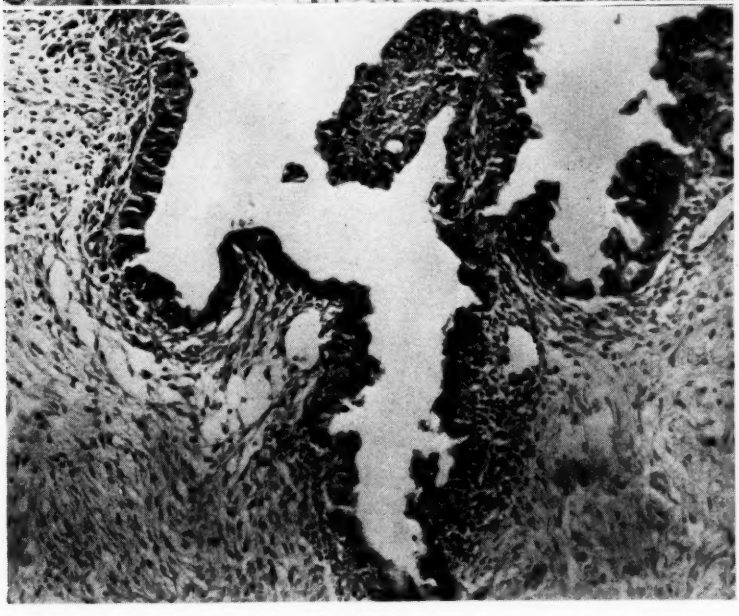

Fig. 3.—Case 1. Lining of endometrial cyst wall.
Fig. 4.—Case 1. Section demonstrating transition of endometrial lining of cyst to adenocarcinoma.

of the tumors lay in the walls of these cysts and were interpreted as having developed from the endometrial tissue. In the other 2 cases, Fredrikson was of the opinion that the malignant tumors were probably derived from endometrial tissue.

In 1947, Novak[12] discussed Sampson's requirements for considering a case one of malignancy arising from an endometrial cyst of the ovary and presented a case which he believed fulfilled these criteria. The transition from benign to malignant epithelium was clearly demonstrated.

Moss and Runals[13] reported the case of a 45-year-old para iii, gravida iii, demonstrating an endometrial cyst with areas of carcinomatous transformation. The predominant appearance of the malignant portions was that of adenocarcinoma such as is found in carcinoma of the endometrium.

McCullough, Froats, and Falk[14] presented a case which appeared to represent adenoacanthoma arising in endometriosis.

Inasmuch as proved cases of ovarian carcinoma arising in endometriosis are exceedingly rare, we wish to report 2 additional cases.

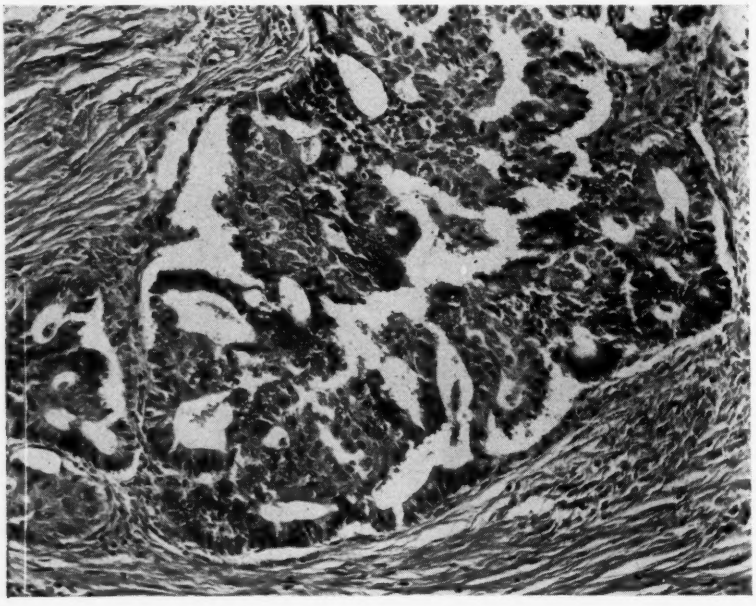

Fig. 5.—Case 1. Area of adenocarcinoma of endometriotic tissue demonstrating squamous metaplasia.

CASE 1.—(Courtesy of Dr. H. G. Thompson.) Mrs. G. V. (No. 725-204), a 44-year-old para iii, gravida iv, was admitted to the Hartford Hospital on May 1, 1952. She had been observed by her family physician for four years because of a "fibroid uterus" associated with menorrhagia. During the preceding two years, the patient had observed a mass in the right lower quadrant of the abdomen. Pelvic examination revealed that the fundus of the uterus was incorporated in bilateral adnexal masses.

At operation on May 2, 1952, the right ovary was found to be replaced by an 8.5 cm. cystic mass which was adherent to the peritoneum in the right cul-de-sac. Pathological study of frozen sections from this mass was reported as Grade I carcinoma. Accordingly total hysterectomy and bilateral salpingo-oophorectomy were performed. The patient was discharged from the hospital on the eighth postoperative day following an uneventful course.

The pathological report stated that the right ovary consisted of an 8.5 cm. cystic mass the inner wall of which was firm, irregular, fibrous, and grayish white. A small cyst measuring 1.0 cm. in diameter was located on the inner wall. This cyst contained a brownish friable material. Microscopic sections of the tumor disclosed extension into and invasion of the stroma by numerous endometrial glands with the characteristic appearance of endometriosis. Some glands were markedly dilated by a bloody secretion. One section of the ovary showed

Fig. 6.

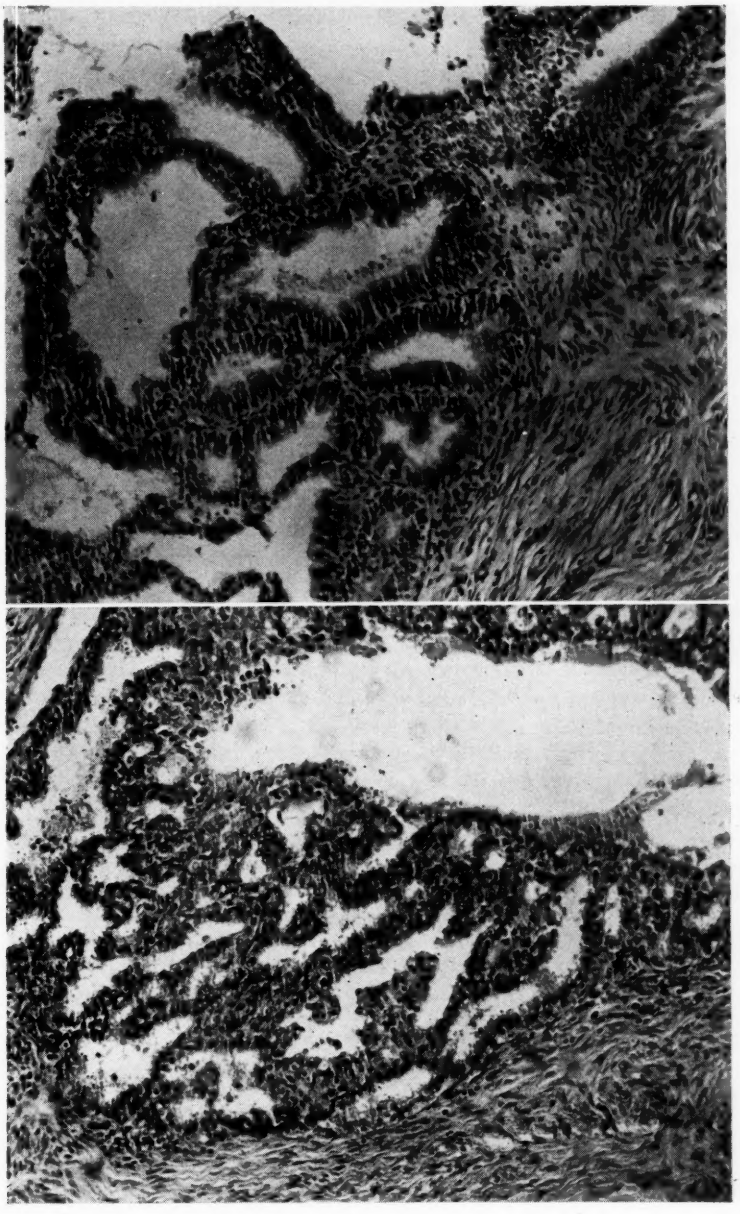

Fig. 7

Fig. 6.—Case 2. Area of endometriosis of the ovary.
Fig. 7.—Case 2. Section demonstrating adenocarcinoma of endometriotic tissue.

papillary adenocarcinoma consisting of cells arranged in a glandular pattern demonstrating numerous mitoses and marked anaplasia. The pathological picture was interpreted as representing malignant changes in endometriosis of the ovary.

CASE 2.—Miss R. P. F. (No. 747-885), a 54-year-old nulligravida, was seen by one of us (J. K.) on Dec. 12, 1952, with a chief complaint of uterine bleeding since November 7. There had been no menstrual period during the preceding eighteen months. Past history was significant in that she had had dilatation and curettage for menorrhagia in 1925.

Physical examination revealed no gross abnormalities. Dilatation and curettage of the uterus was accomplished on Jan. 8, 1953. Examination disclosed that the uterus appeared to be larger than one would expect in a postmenopausal nulligravida. The uterine canal was found to be distorted by an irregular enlargement on the left border of the uterus. A small myoma was palpated on the right anterior portion of the fundus. The cervical canal was dilated with difficulty. A small amount of thick tissue was obtained. Microscopic sections of this material revealed two endometrial polyps composed of a rather cellular but dense stroma throughout which numerous glands lined by columnar cells were noted. The patient was discharged from the hospital on Jan. 9, 1953.

The presence in a postmenopausal patient of endometrial polyps showing evidence of glandular activity made hysterectomy advisable. The patient was readmitted to the Hartford Hospital (No. 755-547) on April 1, 1953. At operation on the following day the uterus was found to be enlarged to twice normal size by virtue of multiple subserous fibromyomas. The left tube and ovary were fixed against the posterior surface of the left broad ligament. The rectum was adherent to the posterior surface of the vagina as the result of endometriosis. A total hysterectomy, bilateral salpingo-oophorectomy, and prophylactic appendectomy were performed. The postoperative course was uneventful permitting discharge of the patient from the hospital on April 11, 1953.

Gross examination of the left ovary which measured 4 cm. in length revealed the presence of a cyst 1.5 cm. in diameter. This cyst showed numerous papillary infoldings of the lining so that the cavity was almost completely filled by the overgrowth. A greenish mucoid material was present in the cyst. The surface of the cyst was smooth and there was no evidence of extension to its external surface. Microscopic sections showed the endometrium to be largely atrophic, but definite polyps with glands in a proliferative phase were seen. The ovarian cyst, described grossly, consisted of a low-grade papillary carcinoma with numerous papillary processes covered by glandular epithelium of columnar type. A slight degree of analpasia with some mitoses was evident. In a few zones a change to squamous epithelium was seen. In one portion of the cyst wall, the glands were supported by a cellular stroma which was suggestive of endometrial tissue. On this basis, the origin of the malignancy from the endometriosis of the ovary was predicated.

There was slight evidence of invasion into the surrounding ovarian stroma, but this was minimal. The external surface of the cyst was free of involvement by the neoplasm.

Comment

Proved cases of ovarian carcinoma arising in endometriosis are exceedingly rare. Hertig and Allan are of the opinion that the carcinoma may arise in association with endometriosis by two means:

1. Malignant transformation of endometriosis.
2. Malignant change in the nonendometrial portion of these mixed cysts.

In both of our cases, it would appear that there had been malignant transformation of a portion of the endometriotic process.

The cases reported herein seem to fulfill Sampson's requirements in that:

1. Both cancer and benign endometrial tissue were present in the same ovary.

2. The cancer and benign endometrial tissue had the same relation to each other that cancer of the endometrium bears to the benign portions.

3. In both instances, the cancer apparently arose in the ovary and did not invade it from another source.

We gratefully acknowledge the kindness of Dr. Hartwell G. Thompson in reviewing this manuscript.

Addendum.—Scott[15] recently reported two cases of carcinoma of the ovary associated with endometriosis. In one case, there was no point in the numerous sections in which the epithelium could be called perfectly benign. The second case apparently fulfills all of Sampson's criteria for interpretation as endometriosis which has become adenocarcinoma.

References

1. Sampson, J. A.: Am. J. Obst. & Gynec. **9**: 111, 1925.
2. Sampson, J. A.: Arch. Surg. **10**: 1, 1925.
3. Meyer, R.: Quoted by Miller, John, in Henke, F., and Lubarsch, O., editors: Handbuch der spezielle pathologischen Anatomie und Histologie, Berlin, 1937, Band VII:3.
4. Corner, G. W., Hu, C. Y., and Hertig, A. T.: Am. J. Obst. & Gynec. **59**: 760, 1950.
5. Allan, M. S., and Hertig, A. T.: Am. J. Obst. & Gynec. **58**: 640, 1949.
6. Scott, R. B., and Te Linde, R. W.: Ann. Surg. **131**: 697, 1950.
7. Teilum, G.: Acta obst. et gynec. Scandinav. **25**: 377, 1944.
8. Kuzma, J. E.: Am. J. Obst. & Gynec. **53**: 245, 1947.
9. Rauramo, M.: Acta radiol. **28**: 638, 1947.
10. Miller, A., Grayzel, D. M., Schiffer, M., and Rosenblatt, P.: Am. J. Obst. & Gynec. **54**: 1022, 1947.
11. Fredrikson, H.: Acta obst. et gynec. Scandinav. **32**: 54, 1953.
12. Novak, E.: J. Mt. Sinai Hosp. **14**: 529, 1947.
13. Moss, L. D., and Runals, A. L.: New York State J. Med. **48**: 401, 1948.
14. McCullough, K., Froats, E. R., and Falk, H. C.: Arch. Path. **41**: 335, 1946.
15. Scott, R. B.: Obst. & Gynec. **2**: 283, 1953.

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THE SEX INCIDENCE OF THE FETUS OR CHILD IN MATERNAL CHORIOCARCINOMA

With Comments on Its Possible Relationship to the Male Trophoblast

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THE object of this study is to tabulate the sex incidence of the fetus or newborn related to the development of choriocarcinoma in the mother with comments on its possible relationship to the male trophoblast. In searching the literature, the sex incidence of the fetus or child was noted to be conspicuously absent in literature surveys of maternal choriocarcinoma. The greatest incidence of choriocarcinoma after pregnancy apparently follows proved or suspected abortions and hydatidiform moles with blighted ova. Twenty per cent of all cases or thirty-four per cent of fatal cases of choriocarcinoma were stated to be preceded by childbirth.[1]

In a search of the records from 1939-1952 of the Los Angeles County Hospital, 5 proved cases of choriocarcinoma in adult women were found. One of the cases followed 5 months after a normal term delivery and no mention was made in the records of the sex of the child. Thus, it was realized that the experience of one large institution would provide insufficient material for this tabulation. Therefore, the accumulated experience of the Albert Mathieu Chorionepithelioma Registry and recently published cases from the literature was sought by means of a questionnaire survey.

The stimulus for this study was a prior interest in the possibility that the placental trophoblast might be endocrinologically sex different; that is, the placenta may be functionally male or female. This appeared to be an explanation for the prenatal sex determination test reported by Rapp and Richardson.[2, 3, 4] Then, too, it was first noted by Symeonidis[6] that choriocarcinoma presented an unusual incidence of distribution, evidenced by a marked preponderance in the testis with only a few rare cases occurring in the ovary. He suggested that the trophoblast of the ovum develops because of influences contributed by the male component in the fertilization process. Hirch[5] reviewed the cases of extragenital choriocarcinoma and found them all to have occurred in males. In the adult woman, choriocarcinoma occurs only as a

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result of pregnancy, that is, by fertilization of an ovum wherein a male and a female sex element are fused. Therefore, Hirsch ventured the conclusion that the trophoblastic tissues are a characteristic of the male germinal tissue, not of mature female tissue, and that the male element contributes the trophoblastic tissue component when choriocarcinoma develops from a fertilized egg as a complication of pregnancy. It seems, then, that this trophoblast-male germinal component relationship may be possibly concerned with the male pronucleus element, and even more specifically with its Y-chromosomal component. The Y-chromosomal component, or male sex determinant chromosome, would be present in the adult female only during pregnancy with a male fetus. All the cells in the adult female contain female sex determinant X chromosomes only.[7, 8] The placental trophoblast, as part of the male fetus, would have the Y-chromosomal component. In the production of choriocarcinoma associated with pregnancy, if all the corresponding fetuses were males, it would prove the trophoblast-male germinal tissue relationship. It would also represent a functional and morphological sex behavior of the placenta implying the male placentas could, and female placentas could not, give rise to choriocarcinoma in the mother. This study, then, is concerned with the descriptive tabulation of the sex incidence (previously neglected in the literature) of a cancer, placental choriocarcinoma, and is an exploration of a possible rationale for a genetic link to the problems of choriocarcinoma, and of the functional sex behavior in general, of the placenta.

Method

A questionnaire was mailed to 58 investigators. This represented 80 cases of choriocarcinoma, which included 72 cases from the Chorionepithelioma Registry, and 8 cases from the recent literature.

Results of Questionnaires

Return correspondence was received on 52 of the 80 total number of cases. Considering that the majority of unreturned questionnaires were from countries outside the United States, this is felt to be a good yield. The recipients of the questionnaires showed sincere attempts at supplying the necessary data. This is indicated by the frequent accompanying letters showing personal interest in the particular case and in the over-all problem. The failure to make or record observations of the sex of the fetus or child was apparent. Thus, in 5 of the 18 cases associated with a term or premature pregnancy, no knowledge of the sex could be found in hospital or office files. In none of the 4 cases associated with an abortion of 4 months or more was the sex recorded. The sex of the fetus usually is evident upon examination of the external genitals after 4 months of development.[8] Nevertheless, in those cases where the sex incidence was recorded, it can be shown (Table I) that in the 13 pregnancies related to choriocarcinoma 8 were females and 5 were males. In this same group the past pregnancy data reveal a sex incidence in the 8 recorded instances of 3 females and 5 males and in the entire series of 52 cases the sex incidence in the 28 recorded instances of past pregnancies is 19

males and 9 females. Evidently there is no definite characteristic sex incidence in the fetus associated with choriocarcinoma. Even from this small series, one can probably deduce that the fetus has approximately an equal chance of being a female or male.

TABLE I. ANALYSIS OF CASES OF CHORIOCARCINOMA IN WHICH SEX OF CHILD IS KNOWN

PHYSICIAN	CHORIOCARCINOMA REGISTRY CASE NO.	SEX OF CHILD	PREGNANCY	TIME ELAPSED BETWEEN DELIVERY AND DIAGNOSIS	TIME ELAPSED BETWEEN DELIVERY AND DEATH	OTHER PREGNANCIES: SEX AND AGE OF CHILD (-NOT KNOWN)
Mason	129	Female	Term	2 months	4 months	None
Winn	141	Female	Term	3 months	8 months	Male, 4
Siegler	153	Male	Term	5 years	5½ years	None
Dempsay		Male	Term	2 months	3 years, 4 months	None
MacRae		Female	35 weeks	2 days	9 days	Males, -6,5; female, 3
Hunter	29	Male	Term	5 months	8 months	None
Hepp	41	Female	Term	5 months	6 months	Male, -4
Floyd	75	Male	Term	4 days	4 days	-3
McCauley	77	Female	Term	2 months	Still living 5 years, 9 months of follow-up	Female, -2
Bartels	90	Female	Term	19 months	20 months	None
Johns Hopkins Hosp.	228	Female	Term	6 months	Still living 1½ years of follow-up	?
Mohler		Female	Premature	1½ months	3 months	Females, -8; M,1
Heller		Male	Term	18 days	18 days	None

Total no. of cases of childbirth pregnancy associated with maternal choriocarcinoma 13
Sex incidence of the newborn: M, 5 / F, 8
Total no. past pregnancies 8
Sex incidence of previous children: M, 5 / F, 3

In the 13 cases with fetal sex recorded, the association of the choriocarcinoma with that pregnancy appears reasonable. In Case No. 153, a period of 5 years elapsed after the associated pregnancy. In another case, 228, the previous pregnancy history is unknown. In view of a possible marked latency period associated with choriocarcinoma following pregnancy, there may be some doubtful association in those cases with past pregnancies, but this is only a meager possibility in view of the rare reported cases. Then, too, one may argue that the stated pregnancy may have represented a multiple pregnancy, one fetus of which was an associated missed abortion. This possibility is small, for there is less than one chance in one hundred, which is the approximate expected incidence of multiple pregnancies,[10] and therefore, it would have no effect on the results in this study.

Two of the patients are still living, one, after 5½ years, and the other, after 1½ years of follow-up. The remaining patients died, evidently from choriocarcinoma, within 4 days to 3½ years after delivery and/or diagnosis, establishing the reliability of the diagnoses in at least 11 of the 13 cases.

Comment

The small number, thirteen, of the cases tabulated with known sex of the fetus or newborn, together with those in which the sex was not observed or recorded, suggests that future cases should be explored for this kind of data, since choriocarcinoma in the mother represents a tumor derived originally from the fetus or child. The sex incidence of tumors is part of the general armamentarium in oncology and it is especially concerned with hereditary and endocrine factors related to the etiology of cancer; nevertheless, the results in this study indicate no male or female sex preference in the fetus for the development of maternal choriocarcinoma. This, then, in terms of the objectives referred to above means that there is no association between the male pronucleus (as related to its Y or sex determinant chromosomal content) and choriocarcinoma. This does not rule out the possibility that other components of the male pronucleus may be related to the development of choriocarcinoma.

The possibility that functionally or endocrinologically the placenta or trophoblast may be sex differentiated remains to be proved. This problem is still worthy of investigation, especially concerning two interesting aspects. The possibility of a prenatal evaluation of the sex of the fetus during pregnancy is one. The other is of broader biological significance and is related to developmental sex determinism. It is most likely that the fetal gonads do not function during early determinant development. Therefore, their hormonal elaboration could not be responsible for the development of the external genitals and thus cannot be related to the occurrence of hermaphrodites and pseudohermaphrodites.[9] The possibility of placental trophoblastic hormonal elaboration playing this role and also the role of the determinism of gonadal sex differentiation exists, and has been unexplored.

Summary

The sex incidence of the fetus associated with choriocarcinoma in the mother shows no definite preference for male or female. Thirteen cases were accumulated from the literature and the Albert Mathieu Chorionepithelioma Registry and the data were obtained by questionnaire. The possibility of a germinal component of the fertilized egg and trophoblast relationship is discussed. This possibility still exists but is probably not related to the presence of the sex determinant component (Y chromosome) in the genesis of choriocarcinoma. The need for further studies concerning the sexual behavior or morphology of the trophoblast (placenta) and its possible implications is suggested.

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References

1. Park, W. W., and Lee, J. C.: Arch. Path. **49**: 73, 205, 1950.
2. Rapp, G. W., and Richardson, G. C.: Science **115**: 265, 1952.

3. Richardson, G. C.: Am. J. Obst. & Gynec. 61: 1317, 1951.
4. Richardson, G. C.: Personal communication.
5. Hirsch, E. F.: Arch. Path. 48: 516, 1949.
6. Symeonidis, A.: Centralbl. f. allg. Path. u. path. Anat. 62: 177, 1935.
7. Patten, B. M.: Human Embryology, Philadelphia, 1946, The Blakiston Company, pp. 56-58.
8. Arey, L. B.: Developmental Anatomy, a Textbook and Laboratory Manual of Embryology, ed. 4, Philadelphia, 1940, W. B. Saunders Company, pp. 48-50, 229.
9. Moore, C. R.: Embryonic Sex Hormones and Differentiation, Springfield, Ill., 1947, Charles C Thomas.
10. Stocks, P.: Acta genet. med. gemellol., Roma 2: 113, 1953.

DIFFERENTIAL EFFECT OF AMINOPTERIN ON THE ACTION OF ESTRADIOL AND PROGESTERONE IN MONKEYS*

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THE inability of estrogens to promote growth in the absence of folic acid has been demonstrated in amphibia, birds, and mammals (Goldsmith and associates,[5] 1948; Hertz and Sebrell,[6] 1944; Hertz and Tullner,[8, 9] 1949, 1950). This dependence of estrogens on folic acid has been shown both in animals maintained on diets deficient in the vitamin and in animals that had received folic acid antagonists. Hertz[7] (1948) found that sexually immature monkeys kept on a synthetic diet free of folic acid would not respond to estrogen after symptoms of vitamin deficiency appeared.

The failure of estrogens to manifest their morphological effects in the absence of folic acid may not apply to other steroid hormones. There is some disagreement as to whether androgens can stimulate growth of the accessory glands of the male reproductive tract in folic-acid-deficient mice and rats (Goldsmith and Black,[3] 1949; Brendler,[1] 1949). However, recent experiments show (Kline and Dorfman,[14] 1951) that stimulation of growth of the seminal vesicles of rats by testosterone is not dependent on the presence of pteroylglutamic acid and that the decreased response previously reported for mice receiving a folic acid antagonist probably was not due to a deficiency of the vitamin but to the concomitant inanition (Goldsmith and Nigrelli,[4] 1950).

It has also been found that folic acid antagonists have a marked inhibitory effect on progestational reactions in the rabbit, rat, and mouse (King and Velardo,[13] 1951) and that Aminopterin is a vigorous inhibitor of progesterone in the development of deciduomas in rats (Velardo and Hisaw,[16] 1953). A point of interest in this connection is that in rabbits and laboratory rodents the action of progesterone on the uterus also can be inhibited quite easily by the simultaneous administration of estrogen (Velardo and Hisaw,[15] 1951) while in primates the two hormones act synergistically (Hisaw,[12] 1950). Therefore, the interaction of estrogen and progesterone on the primate uterus differs from that seen in rabbits, rats, and mice. While it is known that folic acid is essential for the action of estrogen in monkeys and that menstruation can be induced in the castrated animal in the presence of estrogen by giving Aminopterin (Zarrow, Hisaw, and Salhanick,[19] 1950), the influence of folic acid antagonists on the action of progesterone has not been explored.

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With respect to the present experiments, it was thought that a folic acid inhibitor might prove useful in obtaining information regarding the differential action of estrogen and progesterone on the reproductive tract of monkeys.

Materials and Methods

Sexually mature monkeys were castrated and immediately or following the usual postoperative menstruation were given 10 gamma estradiol daily for 20 days. The condition of the reproductive tract of monkeys given such treatment is identical in most respects with that found at the end of the follicular phase of a normal menstrual cycle. Therefore, each animal was subjected to this procedure as a pretreatment for subsequent experiments.

All the animals, following an estrogen pretreatment, were started on a daily routine of an injection of the folic acid antagonist, Aminopterin (4-amino pteroylglutamic acid)* in combination with estrogen or progesterone or the inhibitor plus both hormones. The daily dose for the steroid hormones was estradiol, 10 gamma, and progesterone, 1.5 to 2 mg. This amount of estradiol daily is sufficient to maintain the endometrium indefinitely without uterine bleeding and the dosage of progesterone is adequate for both the prevention of estrogen-withdrawal menstruation and the development of a progestational endometrium.

Among the difficulties encountered in these experiments were those resulting from the apparent extreme sensitivity of monkeys to a lack of folic acid and the wide individual differences in time required to produce a deficiency by giving Aminopterin. These experiences seem to be in agreement with those of Hertz[7] (1948) in experiments in which a folic-acid-deficient diet was used. The problem that arose was that of keeping the animals alive long enough, once a vitamin deficiency was induced, for influences that this might have on the action of estrogen and progesterone to develop. For example, if it were possible to accomplish complete inhibition of estrogen immediately following the twenty-day pretreatment, estrogen-withdrawal bleeding would not occur before about seven days. Also, at the dosage of progesterone used, a period of ten days to a fortnight is required to produce a fully developed progestational endometrium.

Therefore, it was desirable, for the purposes of these experiments, that the animals live for a considerable period in a state of partial or complete folic acid depletion. An attempt was made to accomplish this by starting the animals on a low dosage of the antagonist and increasing the amount every ten days while at the same time following changes in the blood and other symptoms for the appearance of vitamin deficiency. This procedure, however, was not followed in all instances, nor, as the data will show (Table I), was it always successful.

Complete postmortem examinations were made at the end of each experiment which usually was terminated when the animal menstruated or when it was in a state of collapse and near death.

Results

Twelve monkeys were used in these experiments. Following castration and a pretreatment period of twenty days on 10 gamma of estradiol daily, six animals were continued on estrogen in combination with Aminopterin, three were given progesterone and the folic acid antagonist and three received

*Aminopterin (4-amino pteroylglutamic acid) was obtained through the courtesy of Lederle Laboratories, Pearl River, N. Y.

both steroid hormones and Aminopterin (Table I). The most striking result of these experiments is that three of the six animals on estrogen menstruated during the treatment while bleeding did not occur when estrogen and progesterone or progesterone alone was given. Another point of interest with respect to the three animals that menstruated is the lack of correlation between dosage of the antagonist or length of treatment and the time at which bleeding began. Yet, it seems most probable that menstruation was the direct result of folic acid depletion. If so, this again emphasizes the wide individual differences in both dosage of Aminopterin and length of treatment required to produce a folic-acid-deficient state in monkeys.

The six animals used in experiments in which progesterone was included in the treatment showed the same general reactions to Aminopterin and survived for approximately the same length of time as those given the antagonist and estrogen. It seems evident that in both instances the same degree of folic acid depletion was attained. Therefore, the failure of estrogen to maintain the endometrium when Aminopterin is given and the absence of menstruation under similar conditions when progesterone is included in the treatment suggests a difference between the action of the two hormones with respect to dependence upon the presence of folic acid.

TABLE I. EFFECTS OF AMINOPTERIN ON ACTION OF ESTRADIOL, PROGESTERONE, AND COMBINATIONS OF THE TWO HORMONES IN MONKEYS

ANIMAL NUMBER	BODY WEIGHT IN KG.		AMINOPTERIN DAYS AND DOSAGE					MENSTRUATION DAYS OF TREATMENT	REMARKS
	BEGINNING	AUTOPSY	100 μg	200 μg	500 μg	1 MG.	TOTAL DAYS		
Estradiol.—									
157	7.35	5.45	10	10	25	–	45	None	
169	4.52	3.44	10	10	9	9	38	32 to 36	Endometrial repair under way at autopsy
175	3.36	2.31	10	10	28	–	48	42 to 47	No endometrial repair
179	3.77	2.99	10	10	2	–	22	None	
180	3.69	2.69	10	12	—	–	22	None	
181	3.52	2.32	23	—	—	–	23	20 to 23	Yet bleeding at autopsy
Progesterone.—									
167	—	3.56	10	11	29	–	50	None	Endometrium late progestational
178	—	3.07	10	14	—	–	24	None	Enlarged venous lakes
182	3.48	3.17	10	10	—	–	20	None	
Estrogen and Progesterone.—									
172	4.65	3.7	—	—	10	4	14	None	On treatment 8 days before starting inhibitor
176	3.98	3.16	10	11	17	–	38	None	
177	3.98	2.70	10	15	—	–	25	None	Enlarged venous lakes

Monkeys were castrated and given 10 μg estradiol daily for 20 days before the beginning of treatments shown in this table. This dosage of estradiol will maintain the endometrium in monkeys indefinitely without bleeding.

Uterus.—The uterine endometria of the monkeys given 10 μg of estradiol and Aminopterin showed estrogenic effects typical of the follicular phase of a normal menstrual cycle. The endometria of the three animals that menstruated during treatment (169, 175, 181, Table I) showed conditions character-

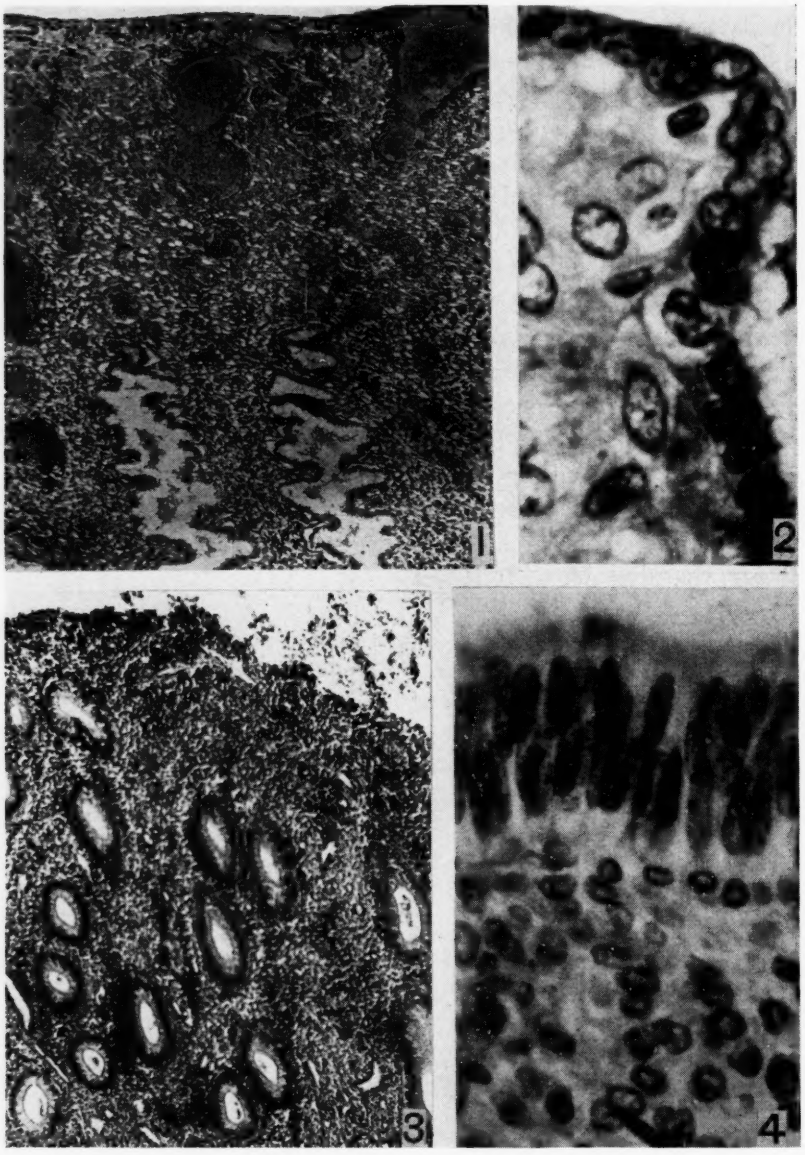

Fig. 1.—Endometrium of monkey 178. Animal was given Aminopterin and 1.5 mg. progesterone daily for 24 days. The endometrium shows a normal progestational reaction with exception of excessive engorgement of the venules and venous lakes.

Fig. 2.—Endometrium of monkey 176, that had received Aminopterin, 10 μg estradiol, and 2 mg. progesterone daily for 38 days. The photograph shows surface epithelium (top), epithelium at mouth of a uterine gland, and underlying stroma. The enlarged stromal nuclei and secretory exhaustion of the glandular epithelium are typical of an advanced progestational condition.

Fig. 3.—Monkey 175. Animal received Aminopterin and 10 μg estradiol daily for 48 days. Menstruation occurred from the forty-second to the forty-seventh day of treatment. The endometrium shows conditions characteristic of estrogen-withdrawal bleeding.

Fig. 4.—Epithelium of a uterine gland and underlying stroma of monkey 181 which had received Aminopterin and 10 μg estradiol daily for 23 days. Menstruation began on the twentieth day of treatment. The epithelium and stromal nuclei show the effects of estrogen.

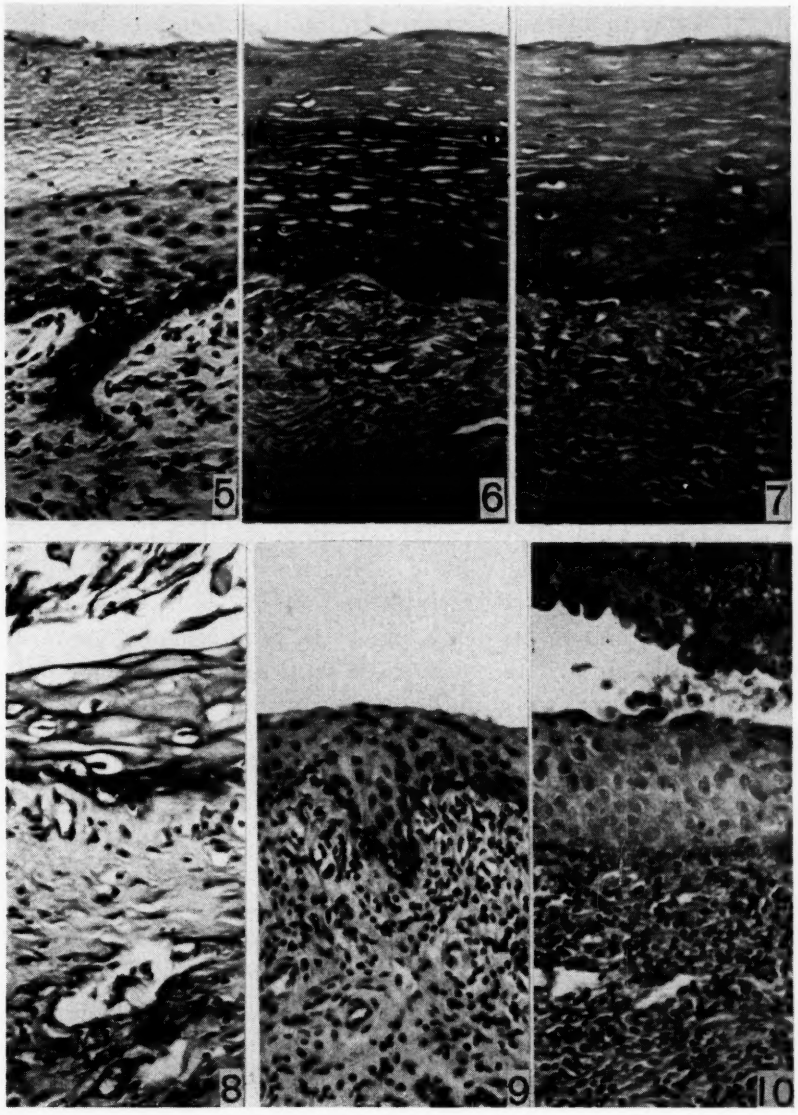

Fig. 5.—Vaginal epithelium of a castrated monkey showing growth and cornification produced by a series of daily injections of estrogen.

Fig. 6.—Vaginal epithelium of monkey 179 which had been given Aminopterin and 10 μg estradiol daily for 22 days. Growth of epithelium almost completely inhibited as indicated by only an occasional mitosis in cells along the basement membrane. Cornification has progressed into the basal layers.

Fig. 7.—Vaginal epithelium of monkey 180 which received Aminopterin and 10 μg estradiol daily for 22 days. Inhibition of estradiol more advanced than that seen in monkey 179 (Fig. 6). Entire epithelium partially cornified and swollen except a few cells along basement membrane.

Fig. 8.—Profound inhibition of growth of vaginal epithelium seen in monkey 175 which had received Aminopterin and 10 μg estradiol daily for 47 days.

Fig. 9.—Vaginal epithelium of monkey 172 which was given Aminopterin, 10 μg estradiol, and 2 mg. progesterone daily for 14 days. Condition comparable with that seen when the two hormones were given without Aminopterin.

Fig. 10.—Monkey 167 which received Aminopterin and 2 mg. progesterone daily for 50 days. Condition similar to that seen in animals given only progesterone.

istic of estrogen-withdrawal bleeding (Fig. 3). In two of these (169 and 175) menstruation began six and seven days before autopsy by which time bleeding had stopped. In both instances repair of the endometrium was under way. The exposed ends of the glands were undergoing active proliferation and a new luminal epithelium had been re-established over large areas of the denuded surface. Mitotic figures in both the surface epithelium and the necks of the glands were quite common. The general condition appeared identical with that seen in endometria in which bleeding had been precipitated by decreasing estrogen below a maintenance dose.

Bleeding did not occur in six animals in the treatment of which progesterone was included. Three of these were given daily injections of 10 μg estradiol, 2 mg. progesterone and Aminopterin, while the other three received 1.5 or 2 mg. progesterone and the antagonist (Table I). The response was the same in both groups in that all animals had progestational endometria of various degrees of development depending upon the length of treatment. Thus it was found that Aminopterin did not prevent a normal response to progesterone as shown by the secretion, coiling, and sacculation of the uterine glands (Fig. 1) and enlargement of the stromal nuclei (Fig. 2) beyond that seen in animals given estrogen (Fig. 4). In two animals (177 and 178) there was marked engorgement of the venules and venous lakes of the functionalis and the formation of numerous hematomas. In both animals, these structures could be seen in the unfixed tissue as dark shotlike objects scattered through the endometrium. Some were undergoing resorption and showed pigment changes, while the surrounding stroma appeared normal, a condition quite different from menstruation.

Vagina.—The vaginal epithelium seems much more sensitive to the inhibitory action of Aminopterin than the uterine endometrium. The growth-promoting action of estradiol on the vaginal mucosa can be completely inhibited. The first noticeable effect of the inhibitor is a decrease in the mitotic activity of the epithelial cells adjoining the basal membrane, followed by what seems to be a complete absence of cell divisions. The thick cornified zone that is invariably present when an estrogen is given becomes less sharply demarcated from the underlying uncornified cells when Aminopterin is added to the treatment (Figs. 5 and 6). This apparently is the result of cessation of mitosis and the addition of new cells to the basal zone of the mucosa and the continuation of cornification. Consequently, the entire vaginal epithelium may become cornified with the exception of a layer one or two cells in thickness along the basement membrane (Fig. 7). The loss of cells from the luminal surface and failure of their replacement by cell multiplication lead to a thinning of the mucosa which in extreme cases may result in almost complete loss of the epithelium over extensive areas of the vaginal wall (Fig. 8).

Aminopterin, also, seems to modify the intracellular process of cornification. The cells are swollen and have distinct limiting borders. The nuclei also are greatly enlarged and when pyknotic the clumped chromatin occupies a clear vacuole. These conditions may be retained in the fully cornified cells that are shed into the vaginal lumen (Fig. 8).

These effects on the vaginal mucosa are strikingly different from those seen when Aminopterin is given in combination with progesterone (Fig. 9) or with progesterone and estrogen (Fig. 10). The cornified zone, present at the conclusion of the period of pretreatment with estrogen (Fig. 5), is lost but the uncornified basal zone persists even when Aminopterin is given for fifty days. In fact, an occasional mitotic division can be found in such epithelia (Fig. 10). These observations are of particular interest in that the effects seen are not unlike those found following a treatment with progesterone or with progesterone and estrogen without Aminopterin. Although estrogen, when included in the treatment, may have been inhibited by Aminopterin, it is true that progesterone also is capable of preventing the cornifying action of estrogen on the vaginal mucosa of monkeys (Hisaw, Greep, and Fevold,[11] 1937). Therefore, in such experiments it is possible that estrogen was doubly inhibited but probably a more important point is, progesterone was not. Thus it is indicated that the action of progesterone on the vaginal mucosa is not inhibited by Aminopterin.

Cervix.—No unusual effects were found in the uterine cervix that could be ascribed to the action of Aminopterin. The glands of the cervix invariably show patches and clumps of metaplastic epithelium, particularly in the basal parts of the glands, following a prolonged estrogen treatment. Such structures were found in the cervices of the three monkeys (157, 169, 175) that had received estrogen and Aminopterin for forty days or longer. Two of these animals menstruated during the treatment thus indicating an inhibition of estrogen. However, this does not necessarily imply complete inhibition as it is well known that menstruation can be precipitated by decreasing the dosage of estrogen below a threshold amount required for maintenance of the endometrium. At the same time, it may be that metaplasia of the cervical glands can occur at a level of estrogenic action below that required for prevention of endometrial involution and bleeding or that, in the cervix, the inhibitory action of Aminopterin is less effective.

The cervical glands of monkeys given Aminopterin in combination with progesterone or with progesterone and estrogen do not seem different from those of animals given only the steroid hormones. They, at least, are alike in that metaplasia of the glandular epithelium is absent. However, progesterone does not induce glandular metaplasia in the cervix and will prevent such effects by estrogen or will bring about the disappearance of such growths when formed by a previous estrogen treatment (Hisaw and Lendrum,[10] 1936). It is interesting to find that in this instance progesterone seems to be a more effective inhibitor of estrogen than Aminopterin.

Comment

Perhaps the most important result of these experiments is the observation that the folic acid antagonist, Aminopterin, is capable of inhibiting the action of estradiol in monkeys but not that of progesterone. This is of additional interest, as far as the uterine response is concerned, since Aminopterin in-

hibits both estrogen and progesterone with apparently equal facility in rats, mice, and rabbits (Velardo,[17] 1951; King and Velardo,[13] 1951; Velardo and Hisaw,[16] 1953). Information adequate for an explanation of this difference is not at hand but it is worth mentioning that decidual and progestational reactions in the uteri of laboratory rodents and rabbits in response to progesterone can be completely inhibited by the simultaneous administration of estrogen, and that this is not true of monkeys. In fact, the concurrent action of estrogen and progesterone in monkeys produces larger uteri and better progestational responses in the endometrium than are attained by progesterone alone. So, in primates estrogen acts synergistically with progesterone in promoting uterine growth rather than inhibiting its influence (Hisaw,[12] 1950).

A possible explanation for these differences is that, in rats, mice, and similar animals, estrogen and progesterone utilize the same enzyme system in producing their metabolic effects, while in primates the two hormones act more or less independently through separate enzyme systems that differ from each other in some important respect. If this be so, then under the first condition one should expect competition between the two hormones for their common enzyme system while under the second this would not necessarily hold. Likewise, if in rodents estrogen is inhibited by Aminopterin, one also might expect inhibition of progesterone, while in primates, if the two hormones utilize separate enzyme systems, this need not apply.

Summary

The influence of Aminopterin (4-amino pteroylglutamic acid) on the action of estradiol and progesterone on the reproductive tract was tested in twelve sexually mature Rhesus monkeys. The animals were castrated and given 10 μg estradiol daily for twenty days after which each received Aminopterin daily beginning with doses of 100 μg and increased after each succeeding ten days to 200 μg, 500 μg, and 1 mg., depending upon the symptoms of vitamin deficiency. During the Aminopterin treatment, six animals were given 10 μg estradiol daily, three received 10 μg estradiol and 1.5 or 2 mg. progesterone, and three 1.5 or 2 mg. progesterone. Three of the six animals on estrogen menstruated during treatment while bleeding did not occur in those receiving progesterone. The endometria of animals given progesterone showed full progestational development. Aminopterin inhibited the action of estrogen on the vagina, had no detectable influence on the response of the cervix to estrogen, and did not modify the response of these structures to progesterone. Therefore, under these conditions, Aminopterin showed a differential action on the effects of estrogen and progesterone on the female reproductive tracts of monkeys.

References

1. Brendler, H.: Science **110**: 119, 1949.
2. Dorfman, R. I.: Recent Progr. Hormone Research **2**: 170, 1948.
3. Goldsmith, E. D., and Black, H. M.: Nature **164**: 62, 1949.
4. Goldsmith, E. D., and Nigrelli, R. F.: Tr. New York Acad. Sc. **12**: 236, 1950.

5. Goldsmith, E. D., Schreiber, S. S., and Nigrelli, R. F.: Proc. Soc. Exper. Biol. & Med. **69:** 299, 1948.
6. Hertz, R., and Sebrell, W. H.: Science **100:** 293, 1944.
7. Hertz, R.: Proc. Soc. Exper. Biol. & Med. **67:** 113, 1948.
8. Hertz, R., and Tullner, W. W.: Endocrinology **44:** 278, 1949.
9. Hertz, R., and Tullner, W. W.: Ann. New York Acad. Sc. **52:** 1260, 1950.
10. Hisaw, F. L., and Lendrum, F. C.: Endocrinology **20:** 228, 1936.
11. Hisaw, F. L., Greep, R. O., and Fevold, H. L.: Am. J. Anat. **61:** 483, 1937.
12. Hisaw, F. L.: in Gordon, E. S., editor: A Symposium on Steroid Hormones, Madison, Wis., 1950, University of Wisconsin Press, pp. 259-276.
13. King, C. T. G., and Velardo, J. T.: Federation Proc. **10:** 208, 1951.
14. Kline, I. T., and Dorfman, R. I.: Endocrinology **48:** 34, 1951.
15. Velardo, J. T., and Hisaw, F. L.: Endocrinology **49:** 530, 1951.
16. Velardo, J. T., and Hisaw, F. L.: Am. J. Physiol. **172:** 535, 1953.
17. Velardo, J. T.: Proc. Soc. Exper. Biol. & Med. **78:** 872, 1951.
18. Zarrow, M. X., Koretsky, I. B., and Zarrow, I. G.: Endocrinology **48:** 125, 1951.
19. Zarrow, M. X., Hisaw, F. L., and Salhanick, H. A.: Science **112:** 147, 1950.

Department of Case Reports New Instruments, Etc.

PULMONARY AMNIOTIC FLUID EMBOLISM

Report of a Fatal Case

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IN 1941 Steiner and Lushbaugh[1, 2, 3] suggested that pulmonary embolism of amniotic fluid might be a cause of sudden maternal death in obstetrical patients. Their suspicion was aroused by the finding of the particulate matter of amniotic fluid (squamae, vernix caseosa, and lanugo hairs) in the pulmonary arterioles and capillaries of certain patients who died suddenly during, or soon after, labor. They were able to reproduce the clinical syndrome of shock and death in laboratory animals by injecting unfiltered amniotic fluid or meconium intravenously. The pathologic findings in the laboratory animals were identical with those in the human autopsy material. More recently, the laboratory work has been repeated and confirmed by Schneider.[4]

The mechanism for the entrance of amniotic fluid into the maternal circulation is clear in the cases of ruptured uterus, cesarean section, placenta accreta, and premature separation of the placenta; but in many of the cases the mechanism is not clear. The case herein reported, which was free of any of the complications of pregnancy, demonstrates a likely portal of entry for amniotic fluid into the maternal circulation.

Case Report

Mrs. A. St. J., a 28-year-old gravida ii, para i, whose expected date of confinement was June 28, 1952, was admitted to the Providence Lying-In Hospital at 2:30 A.M., July 3, 1952, in active labor. Labor began about 11:00 P.M., July 2, 1952. The membranes were intact. The prenatal course had been uneventful. Hemoglobin, blood pressure, and urine were all normal throughout the pregnancy. Her previous pregnancy had been terminated by high midforceps rotation and extraction because of high midpelvic arrest in the right occiput posterior position. The infant weighed 8 pounds, 2 ounces and was normal.

The patient was examined at 3:30 A.M. on July 3, 1952, and at that time the pulse was 92; blood pressure 116/66; respirations 18 per minute; the temperature was 96.6° F. She had symptoms of a mild upper respiratory tract infection with cough, but examination of the heart and lungs was normal. Fetal heart rate was 132 per minute and was located in the midline. The infant presented in the left occiput transverse position with the vertex in the inlet. Rectal examination showed the presenting part high, with the membranes intact and bulging down to the midpelvis. Cervical dilation could not be made out. The pains continued every three minutes, lasting forty seconds. She received medication of Seconal, 6 grains, and Demerol, 100 mg., at 3:30 A.M., July 3, 1952.

At 4:10 A.M. the membranes ruptured spontaneously, with forceful, abundant evacuation of blood-tinged fluid. The patient was immediately brought to the delivery room, talked with the nurses and doctor, and seemed sleepy, but not overly confused.

Fig. 1.

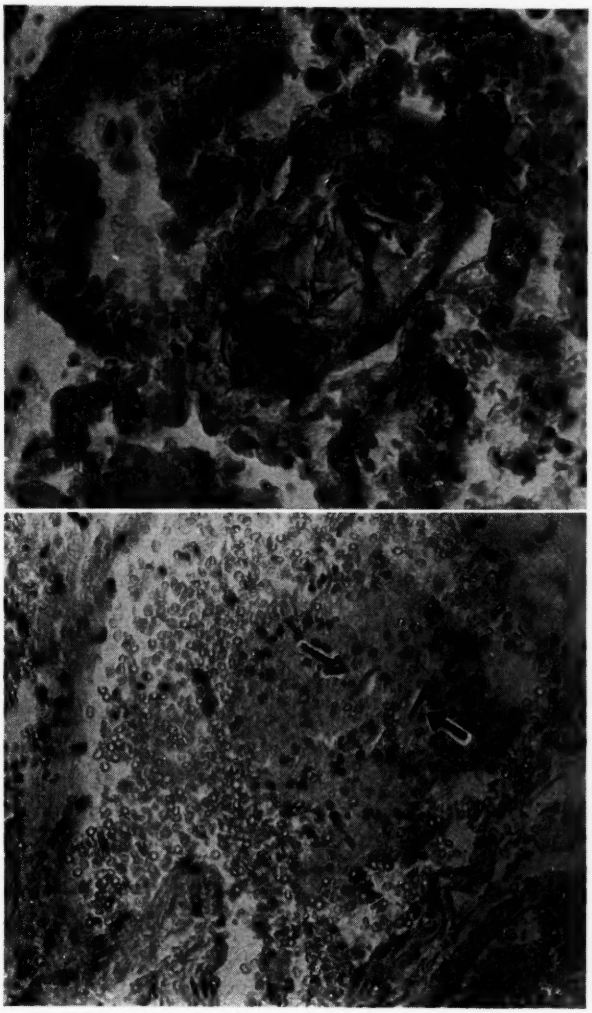

Fig. 2.

Fig. 1.—Squamae in pulmonary vessel.
Fig. 2.—Squamae in uterine vascular sinus.

The fetal heartbeat and the patient's vital indices were, at this time, within the normal range. She was prepared for delivery and suddenly, while receiving 50 per cent nitrous oxide and 50 per cent oxygen, her color became cherry cyanotic and breathing became stertorous. The abdomen seemed rigid and no fetal heartbeat could be heard. An airway was put in place and 100 per cent oxygen administered. No peripheral pulse nor blood pressure was obtainable, but the precordial pulse of about 60 was regular and fairly strongly auscultated. There was no visible vaginal bleeding. A Magill tube was introduced and attached to a Connell machine and bag breathing was instituted with good exchange between the bag and the lungs. The heart suddenly stopped at approximately 4:35 A.M.; intracardiac Adrenalin was given without avail. Artificial respiration was continued for forty-five minutes, and the patient was pronounced dead at 5:20 A.M., July 3, 1952, undelivered.

To recapitulate the time element, the patient died (heart stopped) approximately twenty-five minutes after the membranes ruptured, and about 5 or 6 minutes after she turned cyanotic.

Autopsy showed petechial hemorrhages in the epicardium and blood-tinged pericardial fluid. The lungs were congested and edematous. The uterus contained a 3,300 gram female infant. The placenta was implanted near the fundus. There was a velamentous insertion of the umbilical cord. A small tear was found in the membranes at about the point where the umbilical cord joined the membranes before entering the placenta. The placenta was not remarkable and no evidence of separation, hemorrhage, or infection was seen.

Microscopically, there were focal hemorrhages in the epicardium and in the myocardium and in the myocardium without any inflammatory reaction.

The lungs showed mild chronic passive congestion, edema, and focal hemorrhages. The small arteries were dilated, engorged, and contained large numbers of polymorphonuclear leukocytes. Some of the small arteries contained wrinkled, basophilic-staining squamae, occurring singly or in small clumps (Fig. 1). No lanugo hairs were seen. There was vascular congestion of the spleen, liver, and kidneys. Sections of the uterus taken through the placental site showed squamae in some of the venous sinuses (Fig. 2). Cell blocks made from blood taken from the right auricle and the pulmonary artery also showed many squamae.

Comment

Leary and Hertig,[5] and Landing[6] have shown that premature separation of the placenta, placenta accreta, cesarean section, and rupture of the uterus can open avenues for the entrance of amniotic fluid into the maternal venous sinuses. This case demonstrates another interesting possibility. There was a velamentous insertion of the umbilical cord with a small tear in the membranes at about the place of insertion of the cord onto the membranes. This tear in the membranes, high in the uterus, presumably enabled amniotic fluid, trapped above the engaged fetal head, to be forced out of the amniotic sac. The hydrostatic pressure developed by the forceful uterine contractions could have forced this escaped amniotic fluid into uterine venous sinuses.

This appeared to be substantiated by the finding of squamae in the uterine venous sinuses in the sections taken from the placental site.

Summary

Another fatal case of amniotic fluid embolism is presented. This case demonstrates another probable mechanism for the entry of amniotic fluid into the maternal circulation.

References

1. Steiner, P. E., and Lushbaugh, C. C.: J. A. M. A. **117**; 1245, 1941.
2. Steiner, P. E., and Lushbaugh, C. C.: J. A. M. A. **117**: 1340, 1941.
3. Lushbaugh, C. C., and Steiner, P. E.: AM. J. OBST. & GYNEC. **43**: 833, 1942.
4. Schneider, C. L.: AM. J. OBST. & GYNEC. **65**: 245, 1953.
5. Leary, O. C., and Hertig, A. T.: New England J. Med. **243**: 588, 1950.
6. Landing, B. H.: New England J. Med. **243**: 590, 1950.

CELL GROWTH AND DEHYDROGENASE ACTIVITY: A HISTOCHEMICAL ENZYME STUDY OF PRIMARY SQUAMOUS-CELL CARCINOMA OF BARTHOLIN'S GLAND*

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CARCINOMA of Bartholin's gland is a moderately rare tumor. Te Linde[1] accepted over forty cases as fulfilling Honan's[2] criteria, which include occurrence in Bartholin's gland, origin deep in the labium, contiguity with the gland duct, and apposition to Bartholin's gland tissue. Thirty-eight of these cases are included in Simendinger's[3] review. In this series only nine were squamous-cell carcinomas. In Taussig's[4] classic paper based on 155 cases of vulvar cancer, nine were found arising primarily in Bartholin's gland.

Histologically two types of Bartholin's gland cancer are possible: squamous-cell carcinoma from the superficial ducts, and adenocarcinoma from the columnar- or cuboidal-cell-lined acini and deeper parts of the ducts. Sitzenfrey[6] felt that the transitional and columnar epithelia which line the deeper portions of the ducts may become squamous by a process of metaplasia in the presence of chronic infection, and thus may give rise to squamous-cell carcinoma deep in the gland.

Histochemical studies on the presently reported case are of particular interest in comparison with studies on the far more common and clinically important squamous-cell carcinoma of the cervix. This tumor presented a unique opportunity to have available multiple blocks of squamous-cell carcinoma for histochemical study with a minimum of interference with growth pattern by necrosis and inflammation.

The purpose of this paper is to present some of the histochemical findings in this particular squamous-cell carcinoma.

Case Report

A. T. (No. 80341), a 40-year-old Negro gravida i, para 0, noted a firm mass in the right labium in October, 1952. There was no acute episode, pain, or tenderness connected with the mass and no drainage occurred. In January, 1953, the labial tumor was still present and in addition she now noted a "knot" in the right groin. This inguinal growth was very firm and slightly tender. She consulted her physician who prescribed aureomycin without apparent effect on the size of either tumor. When in February, 1953, the inguinal mass continued to enlarge she sought advice in the outpatient gynecology clinic. There was no history of men-

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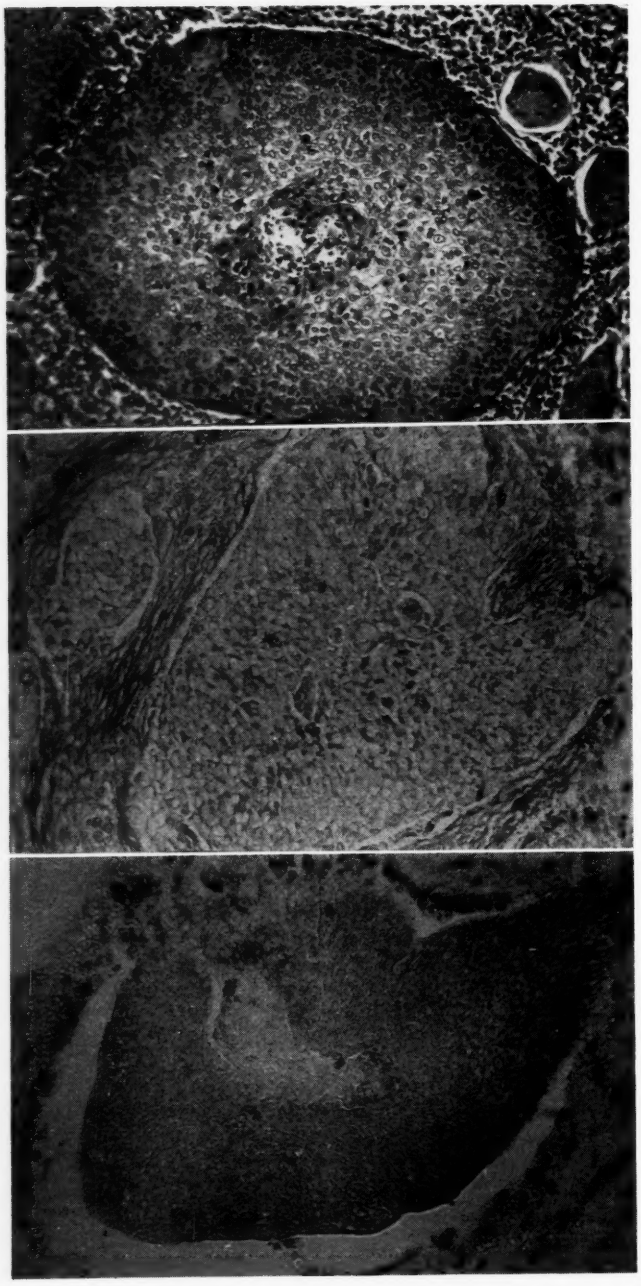

Fig. 1.—*A*, Well-differentiated squamous-cell carcinoma of Bartholin's gland with cell maturation and keratinization toward the center of the neoplastic mass. (×165. Reduced one-fifth.)

B, Periodic acid section. Dark aggregates representing glycogen in tumor cells are more numerous and larger toward the center of the neoplastic mass where cells are more mature. (×165. Reduced one-fifth.)

C, Neotetrazolium section. Granules of formazan represent sites of dehydrogenase activity in tumor cells. The evidence of dehydrogenase activity diminishes toward the center of the neoplastic mass as the cells approach maturity. (×165. Reduced one-fifth.)

strual abnormality. The patient had received treatment for syphilis in 1939 with heavy metals. Otherwise the past history was not significant.

The admission hemogram and chest film were normal. Roentgenograms of the pelvis to rule out calcification of an old Bartholin's cyst were negative. Except for a mild essential hypertension the physical findings were limited to the right labium and inguinal regions.

There was a very firm, movable, nontender nodule in the right superficial inguinal region which measured 4 by 2 by 2 cm. Adenopathy in the left inguinal or other accessible areas was absent. Deep in the right labium occupying Bartholin's area was a hard, nontender, movable mass which measured 4 by 3.5 by 2 cm. The skin was intact over the entire area. There was no surrounding induration or palpable infiltration. A small probe could be passed through the slightly dilated gland orifice into the duct with the sensation of gritty tissue deep in the gland. The opposite Bartholin's gland, Skene's glands, and the urethra were not unusual. The uterus was small, firm, and symmetrical. The adnexa were clear without induration or masses. The cervix was free of lesions.

On March 12, 1953, a wide excision of the right labial tumor was done. The growth measured 3.5 by 3.5 by 1.5 cm., was white in color and very firm in consistency. The excision included the gland, duct orifice, and the surrounding labial integument. A frozen section was reported as squamous-cell carcinoma. At this time a wide Bassett type bilateral groin dissection was done with a labeling of all node localities. Metastases were found in two of nineteen superficial inguinal lymph nodes. One of these nodes containing metastatic tumor was the large palpable right superficial node described clinically. No metastases were found in nine deep right obturator nodes or in seven deep left obturator nodes. Subsequently, on healing of the groin dissection, a vulvectomy was done. The sections of the vulva demonstrated no evidence of residual carcinoma.

Sections of the surgically removed Bartholin's gland and tumor were stained with hematoxylin and phloxine, with periodic acid to demonstrate glycogen,[7] with neotetrazolium to demonstrate sites of dehydrogenase activity,[8] with Sudan black to demonstrate lipid, and for alkaline phosphatase.[9]

The tumor was a fairly well-differentiated squamous-cell carcinoma growing in masses and strands. Most of the larger masses of carcinoma showed some keratinization toward their centers while many had frank epithelial pearls (Fig. 1, *A*). The glandular epithelial structure of Bartholin's gland was seen adjacent, with no essential pathologic change.

The periodic-acid-stained sections showed glycogen droplets in a small proportion of the carcinoma cells. These were more abundant toward the centers of the masses of carcinoma, where the cells had some other evidences of maturation, as, for example, smaller nuclear-cytoplasmic ratios, and keratinization (Fig. 1, *B*). The identity of the periodic-acid-positive substance in the carcinoma cells as glycogen was proved by its absence in control saliva-digested sections.

In the neotetrazolium sections, formazan granules indicating sites of dehydrogenase activity occurred in the cytoplasm of all of the carcinoma cells (Fig. 1, *C*). However, the granules were most concentrated in the cells at the periphery of tumor masses and less densely packed in the cells toward the centers of the sheets of carcinoma. Epithelial pearls showed no evidence of dehydrogenase activity.

Alkaline phosphatase activity occurred only in the nuclei of both carcinoma and stromal cells. No stainable lipid was demonstrated in the tumor.

Comment

This case fulfilled Honan's[2] criteria in that: (a) it occurred in Bartholin's gland, (b) it arose deep in the labium, (c) it was in connection with the gland duct, and (d) it lay in apposition to Bartholin's gland tissue. Further, the skin was intact over the growth.

The histochemical staining reactions were those of a fairly well-differentiated squamous-cell carcinoma. Paucity of glycogen-staining reaction has been

known to students of cervical cancer since the days of Schiller. The failure of intraepithelial cervical carcinoma to reveal histochemical glycogen-staining reaction has been emphasized by McManus and Findley.[7] In their studies adjacent portio vaginalis epithelium showed increasing glycogen deposition as cells matured. The presence of glycogen in cells lying in the central areas of the neoplastic masses in the present case is another indication of its comparatively low grade.

Contrarily, dehydrogenase activity varied inversely to cell maturation. Previously we have demonstrated dehydrogenase activity in sites of growth and proliferation in normal and metaplastic cervical epithelium[8] and in intraepithelial and invasive squamous-cell carcinoma of the cervix.[10] The reverse correlation between glycogen deposition as an index of cell maturity and dehydrogenase activity as an index of cell immaturity should also apply to squamous-cell carcinoma of the cervix.

Summary

A case of squamous-cell carcinoma of Bartholin's gland which fulfilled Honan's criteria is reported. Small amounts of glycogen were demonstrated in tumor cells, increasing with cell maturation. Dehydrogenase activity was found in the neoplastic cells, decreasing with cell maturation.

References

1. Te Linde, R. W.: Operative Gynecology, ed. 2, Philadelphia, 1953, J. B. Lippincott Company, p. 751.
2. Honan, J. H.: Ueber die Carcinome der Glandulae Bartholini, Inaugural Dissertation, Berlin, 1897 (cited by Te Linde[1]).
3. Simendinger, E. A.: Surg., Gynec. & Obst. **68**: 952, 1939.
4. Taussig, F. J.: Am. J. Obst. & Gynec. **40**: 764, 1940.
5. Rabinovitch, J.: Am. J. Obst. & Gynec. **23**: 268, 1932.
6. Sitzenfrey, A.: Ztschr. f. Geburtsh. u. Gynäk. **58**: 363, 1906 (cited by Rabinovitch[5]).
7. McManus, J. F. A., and Findley, L.: Surg., Gynec. & Obst. **89**: 616, 1949.
8. Foraker, A. G., and Denham, S. W.: Surg., Gynec. & Obst. **96**: 259, 1953.
9. Gomori, G.: Microscopic Histochemistry, Chicago, 1952, University of Chicago Press, p. 175.
10. Foraker, A. G., and Denham, S. W.: Texas Rep. Biol. & Med. (In press).

CERVICAL PREGNANCY

Case Report

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RUBIN in 1911 made a complete survey of the subject of cervical pregnancy with a report of seven proved cases. He presented 4 criteria which must be fulfilled to make the diagnosis. (1) There must be cervical glands opposite the placental attachment. (2) The attachment of placenta to cervix must be intimate. (3) The whole or a portion of the placenta must be either below the entrance of the uterine vessels or below the peritoneal reflection on the anterior and posterior surfaces of the uterus. (4) Fetal elements must not be present in the corpus uteri.

Schurger in 1937 was able to find reports of 29 cases recorded up to 1929. He thought there probably were not many more than 30 authenticated cases at the time of this report. His specimen obtained by amputation of the cervix showed the nidation site deep in the cervical wall and apparently about to rupture into the lateral vaginal fornix.

Goodman's and Rubin's cases are of interest from the fact that the corpus showed a well-developed decidua but no evidence of chorionic invasion.

Studdiford in 1944 after a partial review of the literature and a report of two probable cases, reported 14 cases of cervical pregnancy proved by pathological examination of the uterus, obtained at the time of operation or autopsy, in which 4 patients died, a mortality of 28.5 per cent. Also 14 cases of cervical pregnancy based on clinical evidence, in which 2 patients died, a mortality of 14.2 per cent; a combined mortality of a little over 20 per cent. The cause of death was hemorrhage and shock. A good recovery was made in his two cases based on clinical evidence, one patient going on later to be delivered of a normal term infant by low forceps.

From evidence it seems that the site of nidation is in the cervical mucosa. The fertilized ovum traverses the uterine cavity and, having reached the cervical canal, embeds itself in the mucosa. These pregnancies terminate early, because of early degenerative and necrotic changes which occur in the underlying mucosa. These changes account for the early uterine bleeding and early death of the fetus. In response to the pregnancy the cervix becomes highly vascularized; the external os may be dilated. Hence as the placenta develops it becomes anchored to the muscularis. Hemorrhage from rupture of this type of ectopic pregnancy is alarming and very difficult to control. Usually painless bleeding is the first sign of this abnormal pregnancy.

Fig. 1.

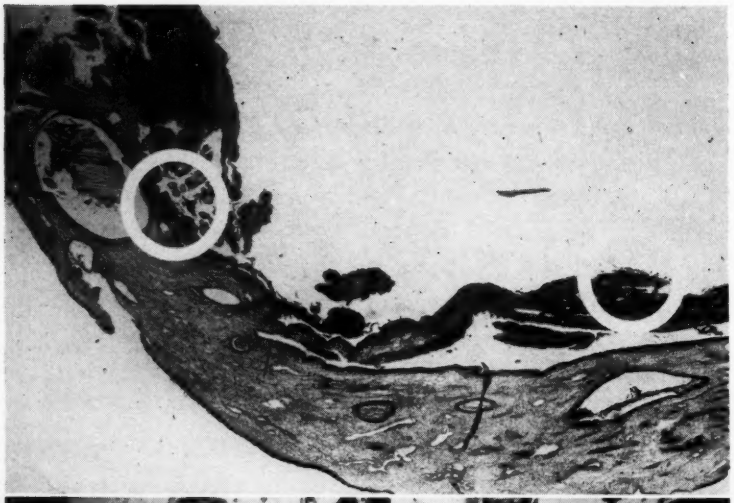


Fig. 2.

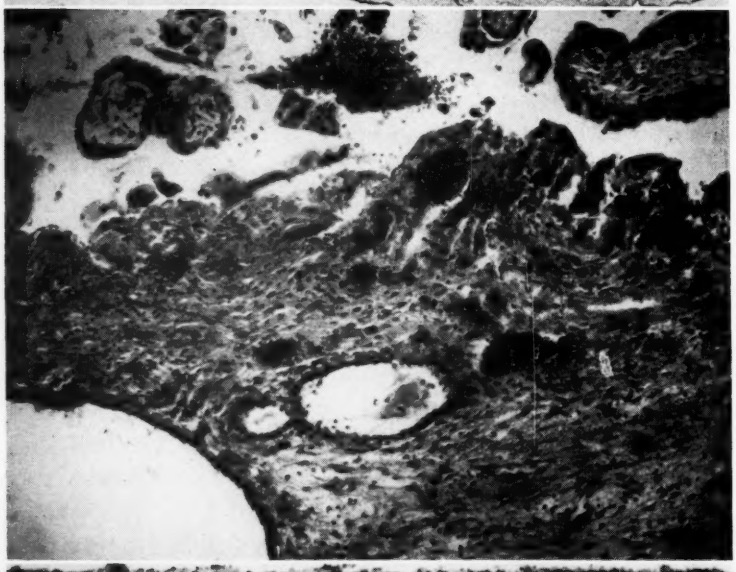
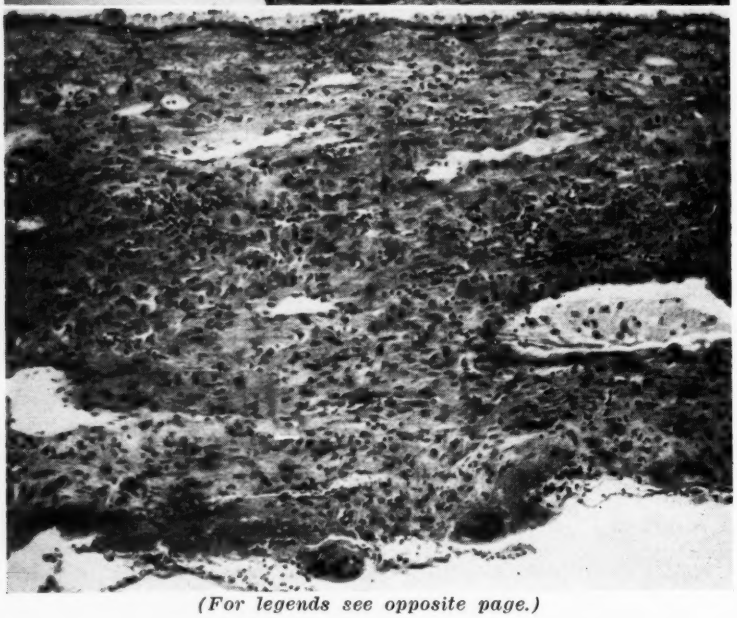


Fig. 3.



(For legends see opposite page.)

Case Report

Mrs. A. S., aged 37 years, para ii, was first seen on Oct. 7, 1952, complaining of frequency of urination and of having menstruated twice in September. Her first pregnancy occurred in 1938 and she was delivered of a normal infant at term by low forceps. The second pregnancy and delivery in 1941 were normal. Her menses had always been regular occurring every twenty-eight days and lasting five days with no pain. The last normal period occurred on Sept. 1, 1952.

General examination was found to be normal. Pelvic examination revealed a good parous pelvic floor. The cervix was posterior, slightly enlarged, firm, and cystic. It contained an old bilateral laceration with a small erosion on the anterior lip. On bimanual examination the corpus was in anterior position, enlarged to the size of three plus months, somewhat softened and irregular. The left ovary was enlarged to approximately 5 by 3 cm. The right ovary seemed normal in size. No tenderness was present.

On October 15 she began to have slight vaginal bleeding which occurred at frequent intervals during the day and night; the next afternoon, a few hours before her admission to the hospital, the bleeding increased. She had no pain. On admission to the hospital she was bleeding moderately. Her temperature was normal, the pulse 80 and blood pressure 130/90. Four hours after admission bleeding became profuse and the patient fainted. The pulse at this time was 100, blood pressure 70/40. A transfusion was given and the pressure rose to 100/70 and the pulse to 82. Bleeding continued. A vaginal examination at this time revealed the cervix to be slightly patulous, and a small, soft, freely movable mass was found barely presenting at the external os. A cervical polyp or a small degenerated cervical fibroid was considered. The onset was so early that no history of amenorrhea was obtained, thus obscuring the diagnosis of pregnancy. Bleeding continued and a complete hysterectomy was advised.

Pathological Report (Dr. Antonio Rottino).—The specimen consisted of a corpus with cervix and left tube and ovary attached, measuring 13 by 7.5 by 5.5 cm. The surface was light brown in color and smooth. When it was opened, the endocervical canal contained dark brown friable tissue which was saclike. On examination, no fetus was visible. The endometrium was brownish white, succulent, granular, and furrowed. The myometrium was grossly normal on section. The ovary measured 5 by 3.5 by 4 cm. The surface was irregular and tense. On being opened it contained a cystic cavity 3 cm. in diameter and contained a yellow serous fluid. The lining was smooth. The tube was dark brown in color. On being opened, the lumen was patent. Also received was a grayish-white saclike structure measuring 2 cm. in diameter. On microscopic examination of the uterus, the endometrium was thick and edematous, glands were in the lutein phase, and the stroma showed decidual reaction. *Cervix:* A portion of the endocervical mucosa was destroyed. Placental tissue with villi was implanted at this site and there was a decidual reaction in the fibromuscular wall of the cervix. *Diagnosis:* Cervical gestation.

References

1. Rubin, I.: Surg., Gynec. & Obst. **13**: 625, 1911.
2. Schurger, A.: Zentralbl. f. Gynäk. **61**: 2584, 1937.
3. Goodman, C.: J. A. M. A. **57**: 1260, 1911.
4. Studdiford, W. E.: Am. J. Obst. & Gynec. **49**: 169, 1945.

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Fig. 1.—Low-power view of endocervix. Glands are markedly dilated. Necrotic placental tissue and blood clot are loosely attached to the wall of the cervix. (×10. Reduced one-third.)

Fig. 2.—Higher power of circled area to the left in Fig. 1. Small nodules of syncytium are attached to the wall. (×100. Reduced one-third.)

Fig. 3.—Higher power of circled area to the right in Fig. 1. Note dilated endocervical glands, villi, syncytial knots and necrosis of the wall of the cervix. (Hematoxylin and eosin stain. ×100. Reduced one-third.)

Editorial

Kosmak Festschrift

The July JOURNAL will be devoted to articles written in honor of Dr. George Kosmak, who was editor of the JOURNAL through the last three decades when medical knowledge was advancing rapidly. Obstetrics and gynecology became a well-established specialty in the United States during this period, an accomplishment to which Dr. Kosmak contributed to no small extent.

All of the articles for the July JOURNAL were written on invitation, some by the colleagues of Dr. Kosmak's years of activity, many by present-day leaders of the specialty in America, a few by outstanding persons from abroad. Articles on most of the important aspects of obstetrics and gynecology today will be included.

The Editors.

Department of Reviews and Abstracts

CONDUCTED BY GEORGE W. KOSMAK, M.D., NEW YORK

Selected Abstracts

Abortion

Swyer, G. I. M., and Daley, Doreen: Progesterone Implantation in Habitual Abortion, Brit. M. J. 1: 1073, 1953.

The authors have studied a series of 113 women who have had two or more consecutive spontaneous abortions. This number was divided into two groups as follows: 60 patients who received single implants of six 25 mg. pellets of progesterone as soon as pregnancy was diagnosed with a successful outcome of the pregnancy in 80 per cent; 53 control patients who were given no specific therapy with 75 per cent success. The successful outcome of the control group of patients is higher than the calculations of Malpas and Eastman. Therefore, the authors question the validity of their estimations.

There were 47 patients with three or more spontaneous abortions who may be designated as "habitual aborters" and these were also divided into two groups: 27 implanted with 47 per cent success and 20 untreated controls who had a 55 per cent successful outcome of pregnancy. The differences between the two groups are not statistically significant. The authors state that these limited data do not give evidence of beneficial effects from the progesterone implantation. Furthermore, the successful result in the untreated patients (55 per cent) was far better than one would expect from the calculations of Malpas, namely, somewhere between 6 and 27 per cent for patients with three or more abortions.

Pregnandiol-excretion studies on both groups of patients provided no evidence of a diminished output in patients with habitual abortion and likewise failed to show any effect after progesterone implantation.

The authors raise the question as to whether or not psychotherapeutic measures contributed to the successful outcome of the pregnancy in treated and untreated groups of patients. They conclude that the prognosis for the untreated patient is much better than has heretofore been supposed.

CARL T. JAVERT

Russell, Keith P.: Changing Indications for Therapeutic Abortion, J. A. M. A. 151: 108, 1953.

The author reports a statistical study of therapeutic abortions performed at the Los Angeles County Hospital during a 20 year period. A total of 295 cases are included in these statistics, an incidence of one therapeutic abortion per 285 deliveries. There were 174 terminations (60 per cent) for pulmonary tuberculosis, 34 (11.5 per cent) for maternal heart disease, and 37 (12.5 per cent) for renal and hypertensive heart disease, accounting for over 85 per cent of all abortions done. Fourteen (4.5 per cent) were done for nervous and mental diseases and 36 for miscellaneous indications. These figures have changed in the past years. Only 2 patients have had abortions in the past two years for pulmonary tuberculosis.

The most frequent method of terminating pregnancy was hysterotomy plus tubal sterilization. During the past ten years, however, there has been a growing use of hysterectomy in cases where sterilization is also desired. The average incidence of therapeutic abortion in the Los Angeles County Hospital 20 years ago was 1 in every 106 deliveries, in the past 5 years 1 in every 2,864 deliveries, and in the past year 1 in every 8,383 deliveries.

WILLIAM BERMAN

Cancer, Malignancies

Hughesdon, P. E., and Fraser, Ian T.: Arrhenoblastoma of Ovary: Case Report and Histological Review, Acta obst. et gynaec. Scandinav. **32:** Supp. **4:** 1, 1953.

The clinical and pathological features of a clinically malignant ovarian arrhenoblastoma are presented in copious detail. The growth was believed to be a mixed mesodermal tumor with celomic, testicular, and Müllerian derivatives, possibly arising directly from the ovarian stroma, so that there are theoretical grounds for disputing, or at least questioning, the accuracy of the diagnosis. The clinical features were those of a masculinizing syndrome and of a malignant tumor with fatal recurrence.

Following the description of their case, the authors present an exhaustive review of the pertinent and related literature, and by quotation of authorities they express the opinion that Robert Meyer's histological (but not histogenetic) view on arrhenoblastomas is broadly correct, but that there may occur, besides testicular tissue, any other mesenchymal pattern. This opinion allows the authors to include their case in the general category of "arrhenoblastoma."

The extensive bibliography is conveniently subdivided into case reports and general references, and constitutes what is, perhaps, the most useful feature of the monograph.

DOUGLAS M. HAYNES

Mammary Glands

Patey, D., and Nurick, A.: Natural History of Cystic Disease of Breast Treated Conservatively, Brit. M. J. **1:** 15, 1953.

For 20 years solitary cysts were treated conservatively by simple aspiration. Four tests are recommended to exclude intracystic tumor which would then require exploration of the breast. First, blood in the aspirated fluid; second, residual lump after aspiration; third, rapid refilling of cyst; and fourth, suspicious cells in smears of the centrifugal fluid.

The authors have traced 65 patients of whom only one has a breast cancer and this appeared in the opposite breast. Of 55 patients followed 2 to 16 years, 20 developed one or more cysts while 35 patients had no further difficulty. From this it is concluded that the tendency to develop cysts dies out. After reviewing 810 cancers for evidence of clinical cystic disease, they concluded that most cancers are not related to this condition.

THOMAS L. BALL

Miscellaneous

Siegel, Irving, and Goldin, Milton: The Sterility of Stored Placental Blood, Obst. & Gynec. **1:** 451, 1953.

The authors describe the collection into A.C.D. solution of blood from 70 freshly delivered ostensibly normal placentas, from each of which 60 to 110 c.c. of blood was obtained, and all of which were cultured for aerobic and anaerobic organisms. Ninety-seven and five-tenths per cent of the blood specimens were found to be sterile; contaminants were found in three specimens. Some difficulty was encountered with hemolysis among the first specimens collected, apparently because of too rapid withdrawal of the blood from the placentas. It is pointed out that complicated deliveries or prolonged labor with ruptured mem-

branes would undoubtedly increase the incidence of positive cultures. The statement is also made, though not substantiated, that placental blood should be more free of the virus of serum hepatitis than ordinary whole blood. The authors feel that placental blood properly collected and handled should offer no greater hazard of contamination than ordinary bank blood. Further studies are being conducted to investigate the immunologic and fractionating possibilities of placental blood. PERRY S. BOYNTON, JR.

Turlington, Lee F., Barclift, W. Clare, and Brown, Hunter M.: A Report on the Cytology of Fifty-eight Hundred Vaginal Smears, South. M. J. 46: 562, 1953.

This report deals with 5,800 vaginal smears from approximately 3,500 patients who have been seen in the private practice of gynecology. During one three-year period (1947-1950) there were 13 patients who had obvious signs and symptoms of cancer of the uterus. Of this group 12 cases were easily diagnosed on the basis of vaginal smears. One case was missed. Recheck of smears on this patient failed at any time to reveal cancer cells. There were 45 cases in the doubtful positive group, 5 of which were confirmed by biopsy or curettage while 40 cases were proved negative for carcinoma.

In this study 3,164 smears were reported as negative for any carcinoma cells. Of this group, 5 patients were shown to have cancer by subsequent biopsies of the cervix or endometrial curettage. In the second group of patients under discussion (1950-1952) there were no patients who had obvious signs and symptoms of cancer. However, in this group there were 6 who showed positive smears and of this group 4 were proved to have carcinoma by biopsy. In the smears which were reported as doubtful there were 4 subsequently shown to have cancer by biopsy or curettage. In the entire group there were 9 cases of carcinoma in situ. Only 50 per cent of this group of cases was diagnosed by means of the vaginal smear, diagnosis being made by biopsy or curettage.

It has been customary in the practice of these authors to advise all patients with even a moderate amount of cervicitis to have the diseased tissue removed by cauterization or conization. In no case so treated has a carcinoma developed in the cervix. There is much difference of opinion among pathologists as to what constitutes the histologic picture of carcinoma in situ. The authors feel, however, that in that case where the diagnosis is made the information should be communicated to the patient and her husband and conservative treatment instituted only upon the condition that the patient will return at frequent intervals for follow-up smears. WILLIAM BICKERS

Martella, Enzo: The Value of the Rana Esculenta Pregnancy Test, Arch. ostet. e ginec. 57: 506, 1952.

The author, from the obstetrical and gynecological clinic at the University of Naples, reviews various pregnancy tests employing frogs and toads. He elected to confine his study to the male of the Rana esculenta. The test was administered by endoperitoneal injection. He reports 858 such pregnancy tests upon the urine of 116 pregnant women with obstetrical complications, 555 normally pregnant women, and 186 nonpregnant women who presented gynecological disease.

The results were found to be correct in 97.56 per cent of the series tested. The earliest positive pregnancy test was that of a pregnant woman following the third day after her missed period. The test was falsely positive in only 1.60 per cent of the series of nonpregnant women who exhibited gynecological disease. All 3 errors were in patients who had pelvic inflammatory disease. Four tables accompany the article. CLAIR E. FOLSOME

Newborn

Murray, J., and Calman, R.: Immunity of the Newborn, Brit. M. J. 1: 13, 1935.

The authors studied samples of cord blood and simultaneous mothers' samples for the presence of antistreptolysin. A streptolysin O was prepared from a Group A III *Strepto-*

coccus pyogenes (strain No. S 84) Copenhagen Serum Institute. After setting up doubling dilutions up to 1:1,280, naked-eye hemolysis was used as the end point.

In 46 cases the antistreptolysin O titer was estimated at the time of delivery. The level in the cord was at least twice that of the mothers in 33 cases; it was higher in 41 cases; about the same in 3; and lower in only one. In one case both levels were too low to be measured. This work now confirms, for a streptococcus, the work of others on diphtherial and staphylococcal antibodies which have been found higher in the cord blood than in the maternal circulation. It suggests that the simple filtration hypothesis regarding placental function for these antibodies is becoming untenable. THOMAS L. BALL

Smith, C. A., Worcester, J., and Burke, B. S.: Maternal-Fetal Nutritional Relationships, Obst. & Gynec. **1**: 46, 1953.

The authors report on a study concerned with the effect of maternal diet on the size and content of certain substances in the fetal liver. The study was based on autopsy material of nonmacerated fetuses and newborn infants who died less than 48 hours after birth. Concentrations of protein, riboflavin, ascorbic acid, vitamin A, thiamine, and iron were studied. Maternal dietary surveys were made according to the Burke Research Dietary History Method. Liver weight increases with fetal age and in general ranges between 3 and 7 per cent of body weight. As the liver grows during gestation, the total amount of protein in the liver increases, and there is an obvious similarity between liver protein concentration at all fetal ages. There was no clearly defined trend in vitamin A concentration although it was slightly higher at 12 to 19 weeks. With respect to ascorbic acid there was a suggestion of a decrease after the nineteenth fetal week. The relatively higher concentration in early fetal life was to be expected since ascorbic acid is known to be more concentrated in rapidly growing tissues. Riboflavin concentrations tended to be somewhat lower in the livers of the youngest fetuses than in those at term. With respect to the content of these three vitamins at term, the values of vitamin A, ascorbic acid, and riboflavin were, respectively, 14 times, 35 times, and 28 times higher than the contents at 12 to 19 weeks. The concentrations of iron in the liver varied irregularly from one gestational age to another. There was no indication in the study that storage of iron results from increasing concentrations. In general the concentration of each of the studied nutrients varied greatly from subject to subject. When dietary surveys of the maternal organisms were made, it was concluded that the fetal liver size is related to dietary intake in the last months of pregnancy, and that liver weight is more related to maternal protein intake than to the over-all diet. There were found to be definite relationships between dietary intake of vitamin A, riboflavin, and ascorbic acid during pregnancy and the fetal content of the maternal diet and the fetal liver content and concentration of these substances. The iron content of the maternal diet and the fetal liver showed no correlation in those cases studied. The authors point out the marked association between low fetal liver vitamin A and maternal intake in those patients who took mineral oil. The authors finally conclude that the weight and composition of the fetal liver reflect maternal intake during pregnancy and probably can be altered by improvement of the mother's diet. DONALD G. JOHNSON

Pregnancy, Physiology

Foraker, Alvan G., and Denham, Sam W.: Succinic Dehydrogenase as an Indicator of Cellular Metabolism in the Cervices of Pregnant and Nonpregnant Women, Surg., Gynec. & Obst. **96**: March, 1953.

Cervical biopsies were obtained from 55 women in normal gestation ranging from the second to the eighth month and from 45 nonpregnant women of a similar age group. These were mostly 6 to 8 weeks post partum. The biopsies were taken from the apparent squamocolumnar junction, without particular search for diseased areas. No qualitative differences in succinic dehydrogenase activity were found between cervical biopsies of pregnant and

nonpregnant women, with the exception of heavy formazan deposition in decidual cells. Since the biopsies from pregnant women had more inflammatory reaction, glandular hyperplasia, and squamous metaplasia with intrinsic evidence of cellular activity, these areas might be expected to show more evidence of dehydrogenase activity. There was no evidence of increased metabolic activity of the portio vaginalis epithelium of the cervix in pregnancy. The authors conclude that if some pregnant women presenting anaplasia of the cervical mucosa have intraepithelial carcinoma, while others do not, we cannot differentiate the two groups, either by morphologic criteria or on the basis of succinic dehydrogenase activity.

WILLIAM BERMAN

Toxemia

Theobald, G. W.: Sympathetic Nerves and Eclampsia, Brit. M. J. 1: 422, 1953.

The author maintains the premise that eclampsia is due to faulty nutrition, together with the mechanical disadvantages associated with the pregnant state. Pursuing this idea, it occurred to him that denervation of the internal iliac vessels might improve the blood supply to the placenta, and so prevent the recurrence of toxemia in succeeding pregnancies. The idea, if effective, might work by increasing the blood supply to the uterus or by cutting off afferent and efferent impulses traveling from and to the uterus through sympathetic pathways. The author describes the surgical procedure whereby the iliac vessels were denervated. Three patients were so treated, two having had two or more pregnancies complicated by severe toxemias with intrauterine fetal death, and a third whose toxemia was considered to have resulted in severe vascular damage. All three patients had successful outcomes of pregnancy following the surgical procedure. The author contrasts two groups of cases with severe toxemias and unsuccessful outcomes of the first pregnancy, but followed either by normal or slightly less than normal subsequent pregnancies, but resulting in living infants. The author believes that such a surgical procedure as described should never be attempted until the patient has passed through two unsuccessful pregnancies even with the most scrupulous care and nutritional guidance. Denervation should be strongly considered with recurrence of toxemia. The author failed in this study to find any evidence that eclampsia was the result of afferent impulses arising in the uterus.

DONALD G. JOHNSON

Agnew, A. M., Palmer, R. A., Bagnall, A. W., and McIntosh, H. W.: Cortisone in the Treatment of Toxemia of Pregnancy, a Study of Four Cases, Obst. & Gynec. 1: 282, 1953.

Four cases of severe toxemia were treated with cortisone as well as other measures, and the responses analyzed.

The first patient developed a fulminating eclampsia with death of the infant in utero. This was followed by anuria and jaundice. Cortisone therapy was given and the jaundice cleared. Azotemia was treated by artificial kidney and the patient ultimately recovered.

Three cases of severe pre-eclampsia were treated with cortisone and the disease apparently was not dramatically affected. One infant died and two were delivered by cesarean section.

The authors feel that cortisone may have had some protective effect on the liver in the case of jaundice and eclampsia, but in the other three cases showed little modifying effect on the course of the toxemia.

JUSTIN CALLAHAN

Correspondence

Anterior Ocular Ovarian Grafts in the Rabbit

To the Editors:

In the December issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY there appears an article by Drs. Ward, Gardner, and Newton on "Anterior Ocular Ovarian Grafts in the Rabbit," which I have read with great interest. However, I regret to say that I noticed that Latin-American bibliography on the subject is unknown to the authors. Six years ago we published results of our studies on this same subject, and later on we studied several mechanisms of the thyroid-genital interrelationship by using ovarian transplants to the anterior chamber of the rabbit's eye as one of the various experimental approaches employed. As it may be of interest to readers of your JOURNAL, I am listing the following references of our contributions on these themes:

1. Arzac, J. P., and Velez Oropeza, E.: Rev. méd. d. Hospital General, México **11**: 208, 1948.
2. Arzac, J. P., and Velez Oropeza, E.: Ginec. y obst. México **3**: 413, 1948.
3. Arzac, J. P., and Guerrero, C. D.: "Interrelacion Tiroide Genital," I Congreso Mexicano de Ginecologia; Mayo, 1949. Memorias editadas por la Asociación Mexicana de Ginecologia y Obstetricia, Mexico, D. F.

While our first impression was favorable regarding the possibility of establishing a practical routine of the Friedman test in rabbits bearing ovarian transplants in the anterior chamber of the eye, later studies made it quite apparent that from a practical viewpoint this was not substantiated. In fact, there is only a relatively short time range in which the castrated-grafted or partially castrated-grafted animals are useful for this particular end as the normal evolution of the graft is to produce automatically hemorrhagic follicles. In the animal bearing its own gonads besides the transplant there are better possibilities, but even so, from a practical standpoint, the advantage in putting an extra gonad from another animal in the test animal is questionable. Moreover, the graft responses in this situation are qualitatively and quantitatively inferior to those of the castrated-grafted animal (before the autogenous hemorrhagic follicles are produced) and to the responses of the gonads in situ of the noncastrated animal.

Nevertheless, this by no means invalidates the extreme usefulness of such an approach for experimental purposes and for research studies of physiological problems, as suggested by the above authors, and as demonstrated by us and by others in the published results on thyroid-genital relationships.

DR. J. P. ARZAC
JEFE DEL LABORATORIO DE ENDOCRINOLOGIA E INVESTIGACION MEDICA DEL HOSPITAL ESPAÑOL

MTE. LIBANE 340
LOMAS MEXICO D. F., MEXICO

JAN. 18, 1954.

Maneuver for Release of the Aftercoming Head in Breech Delivery

To the Editors:

At the suggestion of several of my colleagues, to whom I have described this maneuver, and who, like myself, have found it to be of value, I am sending this description so that perhaps others may use it to advantage.

The obstetrician who has completed the delivery of a breech presentation, with the exception of the aftercoming head, is in a position analogous to that of the anatomist dissecting a hip, trying to remove the femoral head from the acetabulum. In both instances a globoid body is retained in a snugly fitting socket, largely by suction.

I recommend the following maneuver as a supplement to (or in some cases as a replacement for) the use of either the Mauriceau-Smellie-Veit maneuver or the Piper forceps. It has the advantage of being both swift and simple.

With the body of the baby held upward by the ankles with the left hand, the fingers of the right hand are insinuated gently between the baby's head and the walls of the birth passage on the right. If the space is too tight to allow more than one finger, then a single finger is slipped alongside the head to allow air to penetrate the vagina. The finger is moved around the head on that side to break as much of the air seal as possible and to accumulate an air bubble deep to the head. The ankles of the infant are now grasped in the right hand and the maneuver is repeated with the left hand. A lubricant previously applied to the finger tips makes the insertion easier.

This maneuver is accomplished in a matter of seconds and frequently, especially with multiparas, results in a spontaneously released head. Apparently by the breaking of the air seal around the head, and by the formation of an air bubble inside the birth canal, the final phase of delivery is made much easier. If necessary, following this, the usual maneuvers (Mauriceau, or the application of Piper forceps) may be used, but in any case they will be made easier.

MARTIN A. RUSH, JR., M.D.

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JAN. 28, 1954

Items

American Board of Obstetrics and Gynecology

Candidates are urged to make application for certification some time in August or September of 1954, for examinations held in 1955. The deadline date for the receipt of new applications and requests for reopening of applications is Oct. 1, 1954.

It is drawn to the attention of candidates applying for admission to the Part I examinations that they are required to submit a list of all patients for whom they have been *solely* responsible admitted to the hospitals where they practice, for the year preceding their application or the year prior to their request for reopening of their application.

Requests for Applications for Appraisal of Incomplete Training, Applications for Certification, current Board Bulletins, and Preceptorship or Supplemental Training Forms should be made to:

ROBERT L. FAULKNER, M.D., SECRETARY
2105 ADELBERT ROAD
CLEVELAND 6, OHIO

Fellowship in Cancer Research

The Vincent Memorial Hospital, the Gynecologic Service of the Massachusetts General Hospital, announces an American Cancer Society Fellowship in cancer research. Appointment is for one year, beginning July 1, 1954. Further information can be obtained from Dr. Joe V. Meigs, Vincent Memorial Hospital, Fruit Street, Boston 14, Mass.

The American Society for the Study of Sterility

The American Society for the Study of Sterility will hold its 1954 convention at the St. Francis Hotel, San Francisco, on June 18, 19, and 20, immediately preceding the American Medical Association meeting.

The meetings are open to all physicians interested in this field. The registration fee for nonmembers is $10. (Medical students, interns, and residents may register without charge.) Registration should be made in advance by communicating with Herbert H. Thomas, M.D., Secretary, American Society for the Study of Sterility, 920 South 19th Street, Birmingham, Ala.